MN-MED026: HUMAN STUDIES BOARD (HSB) PROCEDURES MANUAL

IMPORTANT NOTICE: A printed copy of this document may not be the document currently in effect. The official version is located on the Medical Documentation page on the Sandia Restricted Network (SRN).

Author: Terry Reser, HSB Administrator, 3333
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Notes: All forms cited in this manual are available on the HSB web site on Sandia's restricted internal network. If you do not have access to that web site, please contact the HSB Administrator to arrange access to forms.

🕮 - indicates a designated procedure

Caveats

No human subject research may begin until reviewed and approved (or determined to be Exempt) by the HSB.

Research that has been approved by the HSB may be subject to further review and approval or disapproval by SNL officials; however, **no individual or committee at SNL may approve or conduct a research project that has been disapproved by the HSB**.

1.0 PURPOSE, AUDIENCE, SCOPE & OWNERSHIP

Purpose

Conducting research on fellow human beings is both a privilege and a serious responsibility. This manual defines specific responsibilities for all persons involved in human subject research for Sandia National Laboratories (SNL).

The purpose of Sandia's Human Studies Board (HSB), known generically as an Institutional Review Board or IRB, is to protect the rights and welfare of research subjects in accordance with applicable laws and regulations, DOE directives, and SNL policy. This manual describes how the HSB accomplishes that purpose through its process and operating procedures.

Audience

The intended audience for this manual includes:

- All members of the HSB
- All principal investigators (PIs), members of any SNL research team that engages in human subject research, and collaborators from institutions outside SNL
- SNL management whose staff engage in human subject research
- The SNL Executive Vice-President, who serves as the institutional official for human subject protection at SNL
- The Sandia Board of Directors
- Members of the workforce at SNL who may participate as subjects in SNL research

Other members of the workforce at SNL will find useful information here about both federal and institutional expectations regarding the development, review, and conduct of human subjects research.

Scope

This manual applies to all activities of the HSB and all research activities that involve human subjects conducted using SNL funds, facilities, or personnel. If the research occurs on SNL premises, this manual applies to all SNL employees, contract personnel, and students regardless of whether the project is funded externally, internally, or receives no funding support.

Ownership

The Chair of the Human Subjects Board owns this document and is responsible for its content. The HSB Administrator is responsible for maintaining the currency and accuracy of this document and for reviewing it at least every three years.

2.0 INTRODUCTION

What is Human Subject Research

Human subject research covers a broad range of activities, and determining what constitutes human subject research is not always straightforward. This section describes the two criteria that define human subject research and provides some examples of what does and what does not constitute such research.

If the answer to both the following questions is "no," then the proposed activity **is not** human subject research. If the answer is "yes" or "I don't know" to either question, then it **may be**. A call to the HSB (845-9171) usually provides a quick answer.

Note: Only *a qualified person or persons other than the investigator or research team* can determine whether proposed research activities qualify for exemption. At SNL, this authority resides solely with the HSB.

1. **Is it Research?**

   Research is any systematic investigation (including research development, testing, and evaluation) designed to develop or contribute to *generalizable* knowledge. "Generalizable" means that new information is added to a body of scientific knowledge or applied to different populations or settings from which it is gained.

2. **Are Human Subjects Involved?**

   Human subjects are living individuals **about whom** a researcher obtains either:

   a. Data through intervention or interaction with the individual, ***or***

   b. Identifiable, *private* information or materials.

   Information is "private" if an individual can reasonably expect it not to be made public (such as medical records) or if the information concerns behavior that the individual can reasonably expect not to be observed or recorded (such as using a public restroom).

Examples

The following activities constitute human subject research and **require HSB approval**:

- The use of bodily materials such as cells, tissue samples, blood, urine, hair or nail clippings, even if the researcher did not directly collect these materials.
- The use of humans to test devices, products, or materials with the express purpose of investigating human-machine interfaces, or to evaluate environmental alterations when humans are the focus of the testing
- Studies conducted to gain knowledge that can be generalized about classes of subjects (such as DOE workers, fast food restaurant workers, women of child-bearing age, etc.).

- Research in which information is obtained either directly from the subject (e.g., oral histories, videos of subjects, interviews, surveys) or indirectly (e.g., observation of human subjects or access to identifiable private records).
- Analysis of identifiable private information even if that information was initially collected for a non-research purpose (e.g., safety and health records).
- Collaborative studies in which material or information related to human subject research is collected at another institution and sent to researchers at SNL.
- Any classified research involving human subjects.
- Projects or pilot studies in which the investigator is the only subject.

The following **do not** constitute human subjects research:

- Studies to improve the safety or execution of procedures that apply to routine occupational activities where the data to be gained is not intended to be generalizable.
- Any research involving information or material from cadavers.

Note: Some human subject research is *exempt* from federal regulations (see Appendix B). However, such research still requires *verification by the HSB that exemption criteria are met*.

When in doubt whether your activities constitute human subject research**, contact the HSB.**

Basic Ethical Principles

Sandia National Laboratories (SNL) is guided by the ethical principles set forth in the report of the National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research, entitled "Ethical Principles and Guidelines for the Protection of Human Subjects of Research" (the *Belmont Report*). These three principles are autonomy, beneficence, and justice.

Autonomy means “respect for persons” and requires that potential subjects be given the information they need, in language they understand, to decide whether or not to participate in a study, and the time and opportunity necessary to make that decision, without any pressure to participate. Autonomy further requires protection of subject privacy, confidentiality of data, and increased protection for vulnerable populations.

Beneficence requires that researchers (and their institutions) do no harm. This includes minimizing the nature, probability, and magnitude of risk while maximizing potential benefits.

Justice requires that the benefits and burdens of research be distributed fairly. Subjects should be recruited based on their relation to the problem being studied rather than their easy availability, their compromised position, or their malleability. Investigators should base inclusion/exclusion criteria on those factors that most effectively and soundly address the research problem. For example, subjects should not be denied access to a study simply because they may not speak English.

SNL Policy

SNL acknowledges and accepts full responsibility for protecting the rights and welfare of ***human***

subjects. **All research that involves human subjects and is conducted using SNL funds, facilities, or personnel must be reviewed and approved by the HSB** and shall comply with applicable DOE Directives and pertinent federal, state, and local laws and regulations. Sandia policy appears in CPR300.5.2, *Protection of Human Research Subjects*.

HSB Mission

The Human Studies Board provides an independent, ethical review of proposed SNL research to assure risks are minimized and reasonable, subject selection is equitable, and subject participation is both informed and voluntary.

3.0 RESPONSIBILITIES

As an institution, SNL bears full accountability for protecting the rights and welfare of ***human subject***s in ***research*** at all SNL sites. However, responsibility for the protection of human subjects is shared between the Institutional Official, the HSB, the Principal Investigator (PI), and the PI's management. To fulfill these responsibilities, all of these individuals must be familiar with HSB procedures and their responsibilities as defined in this manual. Additionally, the Institutional Official, the PI, and all members of the HSB must also complete the Cooperative IRB Training Initiative (CITI) online training. For instructions, check the internal HSB web site or contact the HSB Administrator at 845-9171.

Institutional Official

SNL's Executive Vice-President is the designated Institutional Official for human subject protection. This official is authorized to act for SNL and assumes, on behalf of SNL, the obligations in Sandia's assurance to Health and Human Services' Office for Human Research Protections OHRP (***Federalwide Assurance***, FWA00003764).

The Institutional Official has the following responsibilities:

- Set the "tone" for an institutional culture of respect for human subjects
- Approve and champion SNL policy for protecting human subjects
- Ensure that no research involving human subjects is initiated without HSB approval
- Ensure that SNL-issued solicitations or protocols for research, studies, tests, surveys or other data collection are reviewed to identify research involving human subjects
- Promote communication among SNL staff and management as a means of maintaining a high level of awareness regarding human subject protection
- Encourage participation in human subject educational activities
- Provide sufficient resources, space, and staff to support the HSB
- Support HSB authority and decisions

Human Studies Board (HSB)

The HSB is responsible for reviewing all SNL human subject research submitted to the board and has the authority to approve, to require modifications in (to secure approval), or to

disapprove such research. The HSB is further authorized to suspend or terminate previously approved research that is not being conducted in accord with its requirements or that has been associated with unexpected serious harm to subjects.

HSB members are responsible for attending scheduled HSB meetings, reviewing assigned materials, and participating in HSB discussions. Members should notify the HSB Administrator of a planned absence at least one week prior to a scheduled HSB meeting, and attendance at less than 75% of scheduled meetings during a two-year period may result in removal from the board.

Board members also have the following responsibilities:

- Review proposed research that involves human subjects (see Appendix A, "HSB Initial Review/Approval Process Flow Chart")
- Ensure that research is reviewed at intervals appropriate to the degree of risk, but not less than once per year
- Provide human subject education, information, and training to SNL staff and management
- Be familiar with each of the following:
  - ethical principles of human subject research (Belmont Report)
  - requirements of federal regulations, DOE directives, and applicable state laws
  - SNL's FWA, and *HSB Procedures Manual*
- Have effective knowledge of:
  - subject populations
  - institutional constraints
  - differing legal requirements (e.g., HHS and FDA, federal and state)
  - other factors that may affect risks and benefits to subjects and ***informed consent***

Chair

The HSB Chair ensures that the HSB carries out its responsibilities. In addition to the duties common to all HSB members, the Chair also has the following responsibilities:

- Assure that expedited reviews are conducted in a timely manner
- Keep Institutional Official informed about issues related to human subject research
- Educate HSB members and investigators about their responsibilities
- Report the following promptly to DOE and to the SNL Institutional Official:
  - Any injuries to human subjects
  - Any unanticipated problems involving risks to human subjects or others
  - Any serious or continuing noncompliance with the requirements or determinations of the HSB
  - Any suspension or termination of HSB approval of research
- Ensure that DOE is notified of any new human subjects research involving:
  - an institution without an established IRB,
  - a foreign country,
  - the potential for significant controversy,

- vulnerable subjects (see Appendix F, "Additional Protection for Vulnerable Populations"), or
- the generation or use of classified or sensitive unclassified information

Vice-Chair

The Vice-Chair steps in when the Chair is absent or unavailable. In the capacity of Acting Chair, the Vice-Chair has signature authority for any paperwork that must be processed or decisions that need to be made before the Chair returns. As a corporate attorney, the Vice Chair renders legal opinions on matters related to human subject protection, interprets federal and state regulations and DOE directives, and advises the board as needed.

HSB Administrator

The HSB Administrator manages all the day-to-day activities of the board and is the primary point of contact. The Administrator also has the following responsibilities:

- Function as the primary corporate point of contact for all issues related to human subject research
- Ensure constructive communication among research administrators, management, investigators, human subjects, and Institutional Official
- Make preliminary determinations regarding exemptions and eligibility for expedited review
- Schedule HSB meetings, prepare and distribute agendas and review material, arrange for speakers and other guests, facilitate meetings, and record the minutes
- Coordinate, schedule, and facilitate all reviews.
- Develop and maintain a rotation schedule to assure equitable participation in expedited reviews by all HSB members
- Promptly notify investigators in writing of HSB decisions and requirements for modifications to proposed research
- Maintain copies of all proposed research submitted along with records of HSB determinations, review status, and HSB decisions to approve, disapprove, or require modifications in proposed research, or to suspend or terminate HSB approval
- Document HSB process, philosophy, and procedures for implementing protection of human research subjects at SNL, and maintain currency of this document
- Develop and maintain the following for SNL:
  - Federalwide Assurance (FWA00003764)
  - OHRP registration (IRB00001150, IORG0000793)
  - SNL Policy document (CPR300.5.2)
- Develop and maintain an HSB web site
- Provide orientation for new HSB members
- Provide continuing education material and training for all HSB members
- Provide one-on-one consultation for new PIs

- Provide a copy of this manual to each PI
- Provide ready access for SNL personnel to copies of pertinent federal regulations, policies, and guidelines, as well as SNL policies and procedures
- Inform all HSB members quarterly of all review activity and status of protocols
- Represent Sandia on the DOE Human Subject Working Group (HSWG), at annual national conferences, and on regional IRB Committees
- Keep current on regulations and pending changes that affect human subject protection and advise the Chair, members of the board, and the Institutional Official as needed
- Control access to HSB files to protect data confidentiality and subject privacy
- Prepare and submit an annual report to the DOE Human Subjects Research Database
- Prepare and submit annual summary to HSB Chair and other SNL committees as requested by Chair

Principal Investigator (PI)

The principal investigator has primary responsibility for protecting the rights and welfare of human research subjects and for complying with all applicable provisions of SNL's FWA. Each PI has the following responsibilities:

- Be familiar with the following:
  - ethical principles of human subjects research (see Chapter 2)
  - requirements of federal regulations, DOE directives, and applicable state laws (all of which are summarized in this manual)
  - SNL policies and procedures for protection of human subjects (this document)
- Complete required human subject protection training

  All PIs must be familiar with the information in this manual. PIs submitting protocols for expedited or full board review (see Chapter 5) must also complete the Cooperative IRB Training Initiative (CITI) online training. For instructions, check the HSB web site or contact the HSB Administrator.
- Identify the need to involve human subjects
- Assure that risks to subjects are minimized and benefits are maximized
- Secure director-level approval of research protocols prior to HSB review
- Conduct all research according to an HSB-approved protocol and comply with all HSB determinations
- Ensure that each potential subject understands the nature of the research and of his or her participation, and take whatever steps are necessary to facilitate that comprehension
- Provide a copy of the HSB-approved ***informed consent*** document to each subject at the time of consent, unless the HSB has specifically waived this requirement
- Retain all research-related records, including signed consent forms, that originate with the PI or the research team, for the retention period required by the *SNL Record Retention and Disposition Schedul*e, (Record Series # HR-102-212-000, currently 75 years after completion of the study)

- Provide a copy of this document to each member of the research team conducting human subject research
- Assure that subject privacy and confidentiality are protected
- Promptly submit any proposed changes to previously approved research to the HSB. Do not initiate any change without HSB review and approval, except where necessary to eliminate immediate hazards to the subjects. (See Amendment Review section for more information on proposed changes.)
- Report progress of approved, non-exempt research to the HSB, as often as and in the manner prescribed by the HSB, but not less than once a year. At a minimum, this requires submitting an Annual Review/Continuation Request (FR-MED128) to the HSB Administrator **one month prior to the HSB Approval expiration date** until the study is complete or terminated.
- Promptly report to the HSB any unanticipated injuries or problems involving risks to subjects or others
- Promptly inform the HSB of any new information provided verbally to subjects and provide the HSB a copy of any new written information
- Notify the HSB when project is complete or needs to be terminated
- Provide a summary report to the HSB upon completion of project

PI's Management

Line management is responsible for the preliminary approval and continuing management of research protocols involving human subjects, including the following:

- Evaluate the technical aspects and scientific merit of proposed research
- Validate the necessity of involving human subjects in proposed research
- Assure that proposed research is consistent with research priorities and funding
- Assure that PI has the expertise and experience to conduct the proposed research
- Notify the HSB Administrator when there is a change in PI on an approved protocol.
- Be familiar with SNL policies and procedures for the protection of human subjects (this document)

Note: The PI's Director must approve the HSB Review Form before the HSB Administrator can process it. (see Chapter 5, Step 5.)

Members of the Workforce

All members of the workforce at SNL have the following rights and responsibilities:

- Report any concern or suspected problem with any study involving human subjects to the HSB at 845-9171.
- Report any suspected deviation from an approved protocol to the HSB.

4.0 HSB STRUCTURE

Authority

Federal law, DOE Directive, and SNL policy authorize the HSB to approve, to require modification as a condition of approval, to require additional information prior to HSB review, or to disapprove proposed ***research*** that is within its scope of authority. The HSB also has the authority to suspend, place restrictions on, or terminate any approved protocol.

Jurisdiction

The jurisdiction of the HSB includes all research involving ***human subjects***, data or specimens that:

- is funded by or through SNL, or
- is conducted by or under the direction of any SNL employee, or
- is conducted using any SNL property or facility, or
- involves the use of SNL's nonpublic information to identify or contact human research subjects or prospective subjects

The HSB determines whether or not a research activity falls within its purview and whether it requires review by the HSB.

Composition of Board

The HSB has three executive members: a Chair, a Vice Chair, and an Administrator. The HSB Chair reports directly to the SNL President. The HSB Vice-Chair serves as the Chair in his absence. The HSB Administrator manages all day-to-day activities of the board and functions as the primary point of contact (POC).

The HSB meets the following federal requirements:

- include one Chairperson and at least five members with varying backgrounds
- include at least one scientist and one non-scientist
- include at least one member who is not affiliated with SNL
- is sufficiently qualified through the experience, expertise, and diversity of its members to permit complete and adequate review of research activities commonly conducted by SNL
- is able to ascertain the acceptability of proposed research in terms of institutional commitments and regulations, applicable law, and standards of professional conduct and practice
- when reviewing research involving a vulnerable population, such as children, prisoners, pregnant women, handicapped or mentally disabled persons, the HSB shall include one or more members who are knowledgeable about and experienced in working with these subjects

The HSB may invite individuals with competence in special areas to assist in the review of issues that may require expertise beyond or in addition to the expertise routinely available on the HSB. Such specialists shall not have voting rights.

Selection and Appointment of Members

The HSB Chair and Administrator recruit HSB members from SNL staff (at both NM and CA sites) and from the Albuquerque area community. Names and credentials of prospective members are kept on a waiting list until an opening arises, when they are interviewed by the executive board members. The candidate who is judged the best addition to the board is then recommended for appointment to the HSB.

All members of the HSB are appointed directly by the SNL President for the following terms:

HSB Position	Term
Chair	5 years
Vice-Chair	3 years
Administrator	5 years
Board Members	2 years

All terms are renewable by mutual agreement of the SNL President and the member, and there is currently no limit on the number of terms a member may serve. A list of all board members is sent to DOE and any changes in membership are reported as they occur.

Resignation/Termination of Members 🕮

Members are free to resign from the HSB at any time, but fulfilling existing terms is encouraged.

To remove a member from the HSB prior to expiration of his or her term, there must be documented "just cause" to show that continuation or renewal of a member's term would be detrimental to the board. Just cause for removal may include, but is not limited to, lack of minimum attendance (defined as 75% of scheduled board meetings over a two-year period), misconduct, or unresolved conflict of interest.

Removal of a member whose term has not expired from the Board requires approval of the HSB Chair and SNL's Institutional Official.

Member Training

The HSB Administrator meets with each new board member to describe the operations of the HSB, and what is expected of HSB members. During this orientation, the Administrator also provides the following documents to the member: this *HSB Procedures Manual*, DOE 443.1, and the Belmont Report. All members must complete the Cooperative IRB Training Initiative (CITI) online training. Additional training is provided at each quarterly meeting and through regular mailings from the HSB Administrator (articles, press releases, and newsletters on current issues). The Administrator also maintains a library of reference material and a list of online resources (available from the HSB home page).

Time is allocated on the agenda for each quarterly meeting to address current issues and pending changes in regulations. The HSB Administrator and Chair also use this time to disseminate information gleaned from national meetings and conferences they attend throughout the year.

Member Conflict of Interest

No HSB member may participate in the review of any protocol in which that member has a conflicting interest except to provide information requested by the HSB.

An HSB member is considered to have a conflict of interest when s/he meets any of the following conditions:

- is a member of the research team for the study under review
- supervises any member of the research team or manages the program or organization conducting the study
- has a financial interest in the research with a value that cannot be readily ascertained (this may include equity ownership, stock options, paid consultant fees, or patent, trademark, or licensing agreements)
- has any relationship to the study, the sponsor, or any member of the research team that may be perceived as a conflict of interest

See the "Conflict of Interest" section in Chapter 6 for a general discussion of the concerns related to this area.

5.0 REVIEW AND APPROVAL

Levels of Review

Federal regulations allow for three levels of review: exempt, expedited, and full board. The level of potential risk to the subject determines the level of review required: the higher the risk, the higher the rigor of review.

Note: The **HSB makes the final determination** on which type of review a protocol warrants.

Exempt Review

Certain low-risk ***research*** activities are exempt from rigorous HSB review; however, the HSB still must conduct a preliminary review to determine whether the research meets the criteria for exemption (see Appendix B, "Exempt Research Activities"). This determination can only be made by the HSB (typically by the HSB Administrator, but concurrence by the Chair or other members is sought as needed), and once determined, is in effect only as long as there are no changes in the proposed research.

Even research that has been determined to be exempt must be conducted according to the principles in the Belmont Report.

Note: Human subject research that involves human genetic material is **not** eligible for exempt review.

Expedited Review

This review may be conducted by the HSB Chair or HSB Administrator, a designated voting member, or a group of voting members. During an expedited review, the HSB may approve a protocol, ask for modifications to achieve approval, or refer it to the full board. However, proposed research cannot be disapproved under expedited review.

To be considered for expedited review, proposed research must meet two conditions:

(1) present no more than ***minimal risk*** to subjects, and

(2) fit one of the specific research categories (see Appendix C, "Expedited Review Categories")

Expedited review may also be used for minor changes to approved research.

Full Board Review

All human subject research that does not qualify for Exempt or Expedited review requires review at a convened meeting by a valid quorum of HSB members. This is the highest level of review and to be approved, proposed research must receive the approval of a majority of those voting members present.

Note: No HSB member may participate in the review of any protocol in which that member has a conflicting interest, except to provide information requested by the HSB.

Review Frequency

Human subject research must be reviewed at the following times:

- before the study begins (initial review)
- before any significant changes are made to an approved protocol (amendment review)
- as often as deemed necessary by the HSB, but at least once every year (annual or continuation review)

If proposed research involves no more than minimal risk to subjects, annual review by the HSB is generally sufficient. However, a study involving more than minimal risk may require review more often. To determine whether more frequent review is warranted, the HSB uses the procedure in Appendix G.

Initial Review

The following procedure is also depicted in the flowchart in Appendix A.

HSB Initial Review Procedure 🕮	
Step	**Action**
1.	Principal Investigator (PI) writes draft research protocol.
2.	PI and line management validate need to use human subjects.
3.	PI contacts HSB Administrator.
4.	PI reviews this HSB Manual.
5.	PI obtains Director approval.
6.	PI completes mandatory CITI training.
7.	PI submits ***protocol review package*** to HSB.
8.	HSB reviews proposed study.
9.	HSB approves, tables, or disapproves proposed study.
10.	HSB notifies PI of decision.

The steps for initial review and approval are described in detail below. Procedures for amendment, continuation, and completion/termination reviews are discussed later in this section.

Step 1	Principal Investigator (PI) Writes Draft Research Protocol.

The PI develops a draft protocol to conduct research that will involve human subjects (see Chapter 2 for what constitutes human subject research). Chapters 6 and 7 provide essential information for developing a protocol.

The protocol must reflect what will actually occur in the research. SNL is legally responsible (as are researchers and their supervisors) for research conducted at or sponsored by Sandia, or using SNL's non-public information. Once the HSB has approved a protocol, the investigator is required to follow that protocol or to have any significant change approved by the HSB. The protocol itself becomes a vital part of an official "paper trail" showing that the research is acceptable to a legally constituted board of reviewers. Should anyone question the research, the approved protocol is powerful evidence that the project has sufficient value to justify any risks or inconveniences involved.

Step 2	PI and Line Management Validate Need to Use Human Subjects.

The PI and his or her manager review the proposed research and validate the:

- Necessity of involving human subjects
- Scientific merit of the protocol
- Appropriateness of conducting the proposed study at Sandia (or using SNL funds or personnel)
- Source of funding for the protocol
- Safety issues, including potential hazards to research personnel and subjects
- Expertise and experience of members of the research team
- Availability of departmental resources for the proposed studies
- Scientific processes involved minimize risk to human subjects

Step 3	PI Contacts HSB Administrator.

The PI may contact the HSB anytime prior to this step, but must consult at this point. During this consultation, the HSB Administrator determines jurisdiction and level of review required.

Jurisdiction

The Administrator gathers enough information to determine whether the proposed project (1) meets the definition of "research," **and** (2) involves "human subjects" as defined in federal regulations. Both criteria must be met for the proposed project to fall under HSB jurisdiction.

If both criteria:

are met, the Administrator assigns the protocol an HSB tracking number, opens a protocol review file, and determines level of review (exempt, expedited, or full board).

are not met, the Administrator, with concurrence from the HSB Chair, notifies the PI that the protocol does not constitute human subject research, and does not require HSB approval.

Level of Review

The HSB Administrator (with concurrence from the HSB Chair, as necessary) determines the level of review required (see Levels of Review, earlier in this section).

DOE Notification

The HSB Administrator notifies DOE of any proposed human subject research that involves the following:

- an institution without an established IRB,
- a foreign country,
- the potential for significant controversy,
- vulnerable subjects (see Appendix F), or
- the generation or use of classified or sensitive unclassified information.

Step 4	**PI Reviews this HSB Manual.**

If a proposed study is determined to be human subject research in Step 3, the PI must familiarize himself or herself with the information in this manual and must be able to demonstrate that s/he is familiar with his or her responsibilities as a PI and the HSB procedures described here.

Step 5	**PI Obtains Director Approval.**

The PI's Director must approve all research protocols involving human subjects that require expedited or full board review by the HSB. This approval is indicated by the Director's signature on the Review Request form, which attests that the protocol has been reviewed for:

- scientific merit and design
- the need to use human subjects
- potential Environment, Safety, and Health (ES&H) issues including potential safety hazards to subjects or research team, and waste minimization and disposal, **and**
- source of funding

The Director's signature also signifies that the research team has been evaluated for expertise and experience, and that the PI is qualified to conduct the research.

Step 6	**PI Completes Mandatory CITI Training.**

Before the HSB will accept a protocol review package for Expedited or Full Board review, the PI must complete the Cooperative IRB Training Initiative (CITI) training. This online course may be taken all at once (3-5 hours) or at the PI's convenience. A score of 75% or better is required on the quizzes at the end of each module to pass the course. Upon successful completion, CITI will automatically send a completion certificate to both the PI and the HSB Administrator.

For instructions, check the HSB web site or contact the HSB Administrator.

Step 7	PI Submits Protocol Review Package to HSB.

For the HSB to conduct a review, the PI must submit a ***protocol review package*** that includes the following:

a. A completed **HSB Review Form** (SF 2001-HSB) signed by the PI (all reviews) and his or her Director (expedited and full board reviews). This form is available from the SNL Corporate Forms web site or the HSB home page.

b. A 1-2 page **abstract** of the proposed research, (including a description of risks and benefits).

   DOE requires SNL to provide an abstract for each human subject research project requiring HSB review. The abstract should provide a summary of the proposed project and consist of no more than 750 words. It should be written in non-technical language and clearly explain the PI's role in the research activity.

   DOE posts all unclassified abstracts on a public server. If your proposed study involves sensitive or classified information, notify the HSB Administrator to discuss alternative reporting venues.

c. A complete research **protocol**, including provisions for the protection of human subjects in accordance with all applicable laws and regulations, and any related paperwork (e.g., an activity-specific Standard Operating Procedure, manufacturer's specification sheets, safety reports, etc.)

   Note: For the HSB to approve a protocol, it must reflect a thoughtful design and detailed discussion of all essential elements described in Chapter 6, and must address any applicable special issues described in Chapter 7.

d. A proposed **Informed Consent form** (template available on the HSB web page) that includes all required elements (see "Elements of Informed Consent" in Chapter 6) and is written in plain language understandable by the subject population.

e. Any proposed **recruitment materials** (advertisement, flyer, e-mail, phone script, etc.) for human volunteers.

f. A complete copy of the federal grant/proposal (for federally sponsored studies only)

   Some federal agencies do not require IRB review until the investigator has been notified that funding for the research is likely. Researchers should check with their federal sponsors for guidance. However, researchers are strongly encouraged to contact the HSB Administrator early during protocol development to avoid delays in funding.

g. A copy of any proposed survey or interview script.

h. If the proposed activity is a collaboration with another institution(s), contact information for researchers at the other institution(s) as well as any protocol submitted to the Institutional Review Board (IRB) at that institution(s), and any documentation of review or approval by that (those) IRB(s).

Note: Requests for Exempt review require only "a" and "b"

Step 8	HSB Reviews Proposed Study.

Upon receipt of the protocol package, the HSB Administrator:

a. Verifies that the package contains all required components and all are complete.

b. Reviews package for missing information and items that need clarification.

c. Verifies that any required training has been completed.

d. Schedules a review session (for Exempt and Expedited reviews) or adds the review to the agenda for the next meeting of the full board.

e. Distributes complete protocol package and HSB review checklist to all members participating in the review. Ideally, HSB members receive the review materials one week prior to the review session for Expedited Review and two weeks prior for Full Board Review.

The HSB then reviews the protocol against the criteria in the HSB Reviewers Checklist (FR-MED133).

Step 9	HSB Approves, Tables, or Disapproves Proposed Study.

When the HSB reviews a proposed protocol, it has four options:

- **Approve as submitted**
- **Approve with conditions** (protocol requires minor modifications or PI must furnish minor additional information)
- **Table** (protocol needs major work or lacks sufficient information for the HSB to complete its review)
- **Disapprove** (protocol does not meet the minimum criteria required for approval)

Approval

To approve a research study, the HSB must ensure that ***all*** of the following requirements have been satisfied:

- Risks to subjects are minimized and reasonable in relation to anticipated benefits.
- Selection of subjects is equitable.
- Participation is voluntary and informed consent will be sought from each subject and appropriately documented.
- Adequate provisions are made to protect subject privacy and confidentiality of data.
- When any subjects are likely to be vulnerable to coercion or undue influence, additional safeguards are included to protect the rights and welfare of those vulnerable subjects.

Conditional Approval

If the HSB grants conditional approval pending changes to the protocol, such changes must be completed before the HSB Chair will certify final approval of the protocol. Alternatively, the HSB may approve, but impose certain restrictions or conditions on the researchers or on the conduct of the research (e.g., HSB may require third-party observation of the consent process).

Conditional approval requires three steps:

1. HSB specifies conditions (in writing to the PI).
2. PI meets conditions and provides HSB evidence of same.
3. HSB verifies that conditions are met.

Note: If verification cannot be made, the protocol cannot be approved.

The HSB Administrator will notify the PI (via e-mail, within five business days) of any issues or concerns identified during the HSB review.

Approval Period

When it approves a study, the HSB must also determine how often it needs to be re-reviewed. The maximum approval period is one year, and is used for studies that are determined to be no greater than minimal risk. Studies that have potential for greater than minimal risk shall be evaluated using the procedure in Appendix G, "Procedure to Determine Review Frequency," and meeting minutes should reflect this determination.

Step 10	HSB Notifies PI of Decision.

Notice of Approval

Once all HSB conditions for approval have been satisfied, the HSB Administrator prepares a Notice of Approval (FR-MED130), which specifies the HSB approval date and the date that approval expires.

Note: The approval date is the date the proposal was reviewed and conditionally approved by the HSB, not the date when required conditions were met by the PI or accepted by the HSB.

A protocol can be approved for a maximum of one year. If the HSB specifies conditions for approval, the approval period does not begin until those conditions have been met. For example, if a PI takes two months to comply with conditions, the approval period may not exceed 10 months.

This notice summarizes the major requirements the PI must meet while conducting the research; however, the PI must be familiar with all responsibilities specified in Chapter 3 of this manual. Where applicable, the Notice of Approval is accompanied by an approved informed consent form bearing the HSB approval stamp and expiration date. The PI is instructed to safeguard this stamped and approved form, since only copies of the currently approved form may be used in the consent process.

Tabled Study

When the HSB tables a protocol, it must specify what specific information is missing or needs more development, or what issue needs to be resolved before the HSB can proceed. The HSB Administrator notifies the PI of the board's determination. Until the PI provides that information and/or revises the submitted materials, the board can take no further action, and no activity may begin on the study.

Disapproved Study

If a study is disapproved, the HSB Administrator notifies the PI in writing and must specify the reason(s) for the disapproval so that the investigator has an opportunity to respond (in

person or in writing).

Note: Research that has been approved by the HSB may be subject to further review and approval by SNL officials; however, **no individual or committee at SNL may approve or conduct a research project that has been disapproved by the HSB**.

Amendment Review Procedure 🕮

Any significant change to an approved protocol requires HSB approval **prior to implementing**. Such changes include, but are not limited to:

- Any change that alters the stated risks, unless the change is necessary to eliminate an apparent immediate hazard to the human subject(s)
- Any change in personnel or job assignments that affects the protocol. (e.g., change in PI or co-PI, change in who recruits or interacts with subjects)
- Any change in subject population
- Any change that alters the specific aims, design, or scope of the study

HSB Amendment Review Procedure 🕮	
Step	**Action**
1.	The PI submits a Request to Amend Approved Protocol form (FR-MED132) to the HSB Administrator. This form (available from the HSB home page) requests a complete description of the amendment, as well as justification for the change, and an evaluation of how this proposed change may affect risks or benefits to subjects. This form must be accompanied by a revised protocol with all proposed changes highlighted in the text, and a revised informed consent form, if necessary.
2.	The HSB Administrator reviews the package for completeness and accuracy.
3.	The HSB Administrator (with concurrence from the HSB Chair or Vice Chair if the Chair is not available) determines whether the proposed amendment has affected the level of review required.
4.	The HSB follows Steps 8, 9, and 10 (above) from the initial review.
5.	The HSB Administrator retains a copy of all documentation submitted for the amendment, along with the approval or disapproval, and any related notes, or required conditions in the HSB protocol file.

The only exception to this requirement would be a situation where a change in an approved protocol was necessary to eliminate immediate hazards to the subjects. In such an instance, the PI must report the change to the HSB immediately.

The HSB may only approve amendments submitted during a current approval year, and the approval period remains the same as in the initial review, unless the HSB chooses to shorten it as a result of the change. For example, if a new or annual review takes place on May 1, 2008, the original protocol will have an expiration date of April 30, 2009. If an amendment is approved on

February 28, 2009, the expiration date still remains April 30, 2009.

Each revision to a protocol must be incorporated into the written protocol. This practice ensures that there is only one complete protocol with the revision dates noted on each revised page and the first page of the protocol itself. If revisions are too extensive for this to be practical, then a new protocol should be submitted. This procedure is consistent with the procedure used for revised informed consent documents, which supersede the previously approved one.

Continuation Review

Every ongoing research protocol approved by the HSB must be re-reviewed at intervals appropriate to the degree of risk, but at least every twelve months. The expiration date for HSB approval is determined by the HSB at the time of the initial and/or amendment review, and is indicated on the Notice of Approval sent to the PI.

It is the investigator's responsibility to ensure that the research is reviewed on or before expiration of the current approval period, even if the research activity did not begin until some time after the IRB gave its initial approval. To avoid expiration of HSB approval, the **PI must submit an "Annual Review/Continuation Request"** (FR-MED128) **at least one month prior to the expiration date** of the existing HSB approval.

Note: If a PI fails to submit FR-MED128 prior to the HSB Approval expiration date, the study will be suspended (see 'Suspension of HSB Approval" in Section 9.0, Monitoring).

Continuation review and approval is necessary if recruitment of new subjects stops but previously enrolled subjects continue to participate in the research, or even when subject participation has ceased but data analysis continues on the study.

Additionally, the HSB may be called into an interim review session by the HSB Chair at the request of any HSB member to consider any matter involving the rights and welfare of any subject.

HSB Continuation Review Procedure 🕮	
Step	**Action**
1.	The PI submits a completed Request for Continuation Approval (FR-MED128) **one month before the expiration date of the current HSB approval**. This request, available from the HSB web site, must include the following information: • a copy of the current consent document • a description of any adverse effects or unanticipated problems • the number of subjects studied since the last approval • the number of subjects withdrawn and reason for withdrawal • any new information that may affect subjects' desire to continue participation • any change in funding since the last approval
2.	The HSB reviews the above information **and** the following: • any amendments and their status • reports of any adverse events

HSB Continuation Review Procedure 🕮	
Step	**Action**
	• any complaints about the research • any findings, published or in press • any other relevant information
3.	The HSB evaluates whether anything has changed since the last review to cause concern about re-approving the study. If not, the approval proceeds. If so, the HSB investigates whether additional information is needed and what, if any, additional safeguards need to be implemented to mitigate any new risks or address new information.
4.	The HSB Administrator notifies the PI of the results of the review and processes appropriate actions.

Completion/Termination Review 🕮

Upon completing a study or when a PI needs to terminate a study before it is complete, the following procedure must be used.

Note: A study terminated by the PI only needs to be reported to the HSB, unless it is out of compliance, in which case it may need to be reported to others as well. See "Suspension/Termination" in Chapter 9.

HSB Completion/Termination Procedure 🕮	
Step	**Action**
1.	The PI submits a completed Request for Completion or Termination of an Approved Protocol (FR-MED129) This request, available from the HSB web site, must include the following information: • whether the study is complete or to be terminated • the number of subjects studied since the last approval • the number of subjects who were excluded • the number of subjects withdrawn • a description of any injuries or unanticipated problems • any change to the previously approved protocol
2.	The HSB reviews the above information **and** the following: • reports of any adverse events • any complaints about the research • any other relevant information
3.	The HSB evaluates whether there are any remaining issues, including any reporting not yet completed that need to be resolved before completion or termination. If not, the approval proceeds. If so, the HSB investigates whether additional information is needed and what, if any, additional actions need to be taken.
4.	The HSB Administrator notifies the PI of the results of the review and processes appropriate actions.

HSB Completion/Termination Procedure 🕮	
Step	**Action**
5.	The PI also must submit a final report or summary report to the HSB. However, since this may be in the form of a published article, this requirement may be met after the study is officially closed.

6.0 RESEARCH DESIGN

Certain elements of research design figure prominently in the HSB's review of a protocol. This chapter discusses those elements that the HSB considers essential to an approvable protocol. A protocol that doesn't sufficiently address these issues will likely be tabled and sent back to the PI for more information.

Background and Description of Research

Include the following elements:

- The title and sponsor (funding source) of the study.
- The purpose of the research and the hypotheses to be tested.
- The historical background of the research, citing pertinent scientific literature.
- An orderly account of the research method, design, and mode of analysis, detailed enough that reviewers can assess scientific validity. Include a complete description of procedures that directly affect subjects.
- A realistic statement of the value of the research, including both what the researcher expects to learn from the research and how it might benefit (a) the participants, (b) their community, (c) SNL, (d) the sponsor, and/or (e) science or humanity in general.
- The location of the research – indicating the exact facility(ies) where the research will be performed and why that setting was chosen.
- The duration of the project and, if applicable, a timeline for different phases.

Subject Recruitment and Selection

Include, where relevant, ethnic background, sex, age, and state of health of intended subjects. Explain why a particular population is being used, the pool(s) from which subjects will be recruited, and a statement of the inclusion/exclusion criteria to be used.

Caution: If a proposed project is open to the general SNL workforce, it may involve student interns who are considered minors. See "Special Subject Populations" in this chapter and "Additional Protections for Vulnerable Populations" in Chapter 7.

Recruiting Subjects

Recruitment is the dialogue that takes place between an investigator and a potential subject prior to the start of the consent process. Recruitment procedures that ensure voluntary and informed participation ensure respect for human subjects. The HSB is required to review any recruitment material that may be used (e.g., posters, flyers, newspaper ads, press releases, brochures, e-mail and web postings). These materials should include:

- the name of the investigator and contact information
- the purpose of the research
- general eligibility criteria
- a truthful description of any potential risks and benefits
- the frequency and duration of subject involvement

Selecting Subjects

The HSB will disapprove any proposed research that selects subjects solely because of their easy availability, compromised position, or susceptibility to manipulation. Potential subjects should not feel coerced into participating, nor fear the loss of some benefit to which they are otherwise entitled if they choose not to participate, to end participation before a study is concluded, or to report an adverse event.

Investigators proposing to recruit and select direct reports, students, or other co-workers as research subjects must justify the necessity for including these individuals. The protocol should clearly articulate what steps will be taken to avoid the potential for coercion when selecting subjects who are in a dependent or peer relationship to the investigator. (See "Co-workers as Subjects," in Chapter 7.)

Limiting a subject pool to fellow workers may also invite a "self-fulfilling prophecy" situation and raise questions about the credibility of both the study design and the data collected.

Risks and Benefits

Discuss the potential risks including inconveniences or discomforts, and where possible, estimate both the likelihood and the magnitude of harm. The description of benefits of research should take into account potential benefits a subject may derive from participation in research, and/or the benefits of new knowledge that may justify asking a person to undertake the risks of the study.

Note: Payment for participation in research **is not** considered a benefit, but rather compensation for research-related inconvenience.

The HSB will assess whether the risks of the study are offset by the benefits. Some biomedical research presents risk of physical injury to subjects. Although most of these risks are transient, some adverse effects of participation may result in permanent injury to subjects. For research with the potential to cause physical harm, investigators should think through all risk possibilities, however rare, so that they can be resolved quickly and effectively minimize the harm to subjects. Clearly detailing procedures to address situations of physical harm will assure the HSB that the PI has made efforts to minimize physical risks to the greatest extent possible.

However, not all risks are physical. Some research involves collecting sensitive information that may result in injury to subjects through a breach of confidentiality. These breaches may result in

embarrassment within a subject's business or social group, loss of employment, or criminal prosecution. Any research protocol that involves information regarding drug and alcohol use, mental illness, sexual behavior, or illegal activities should clearly detail strong safety precautions to ensure that the research does not cause social or economic risks to the subjects.

The "Common Rule" for the Protection of Human Subjects (10 CFR 745) requires that:

- "Risks to subjects are minimized: (i) By using procedures which are consistent with sound research design and which do not unnecessarily expose subjects to risk ..." and
- "Risks to subjects are reasonable in relation to anticipated benefits, if any, to subjects, and the importance of the knowledge that may reasonably be expected to result."

The federal Office for Human Research Protections (OHRP) interprets these requirements to mean that "If a research study is so methodologically flawed that little or no reliable information will result, it is unethical to put subjects at risk or even to inconvenience them through participation in such a study." Accordingly, HSB review includes a consideration of whether the study meets some threshold of scientific merit.

Privacy and Confidentiality

Privacy refers to *persons* and to their interests in controlling the access of others to themselves. Confidentiality is an extension of that concept and refers to how *data* should be protected to control the access of others to information about the subject. Ideally, confidentiality is handled in the informed consent form, which is an agreement between researcher and subject. That agreement states what may be done with private information that the researcher collects on the subject, and the terms of the agreement should be tailored to the particular situation.

Investigators are required to protect the privacy of subjects and the confidentiality of subjects' data, except as required by law or released with the written permission of the subject. [10 CFR 745.111 (a) (7)]. Subjects have the right to be protected against invasion of their privacy, to expect that their personal dignity will be maintained, and that the confidentiality of private information will be preserved. The more sensitive the research material, the greater the care required in obtaining, handling, and storing data.

Information through which subjects may be identified include their names, employee numbers, hospital ID numbers, social security numbers, driver's license numbers, home addresses, photographs, videotapes, and the like. Individuals also may be identified by job description, (e.g., the manager in the Human Resources Department, or the sixth grade teacher at a certain school). If information to be collected can be traced back to individual subjects, safeguards should be provided to ensure confidentiality.

Researchers should consider how the data and links to subjects will be stored and maintained, as well as whether or not they will (1) provide information about subjects to others not involved in the research, and (2) provide information they have learned about the subjects to the subject. Researchers should also consider to what extent a breach of confidentiality or invasion of privacy would constitute harm.

Note: No legal privilege exists between investigator and subject as it does between physician and patient or counselor and client. Thus, a guarantee of confidentiality cannot be given

or implied. However, PIs can protect confidentiality "as far as possible under the law."

The only way to protect research records from subpoena is through a Federal Certificate of Confidentiality. If such a certificate is obtained, the consent form should briefly describe the added degree of protection that this certificate provides. For more information on certificates, see this web site.

Researchers must also consider whether the data generated in the study is likely to be used in future research, and to indicate that likelihood in the consent agreement.

Rules of Thumb for Protecting Confidentiality

- Only record personal information that is essential to the research.
- Restrict access to personally identifiable data to the research team.
- Do not disclose personally identifiable data to anyone outside the research team without the written consent of the subjects, unless required by regulations.
- Code data as early as possible, and plan for the eventual disposition of the code linking the data to individual subjects.
- Apply for a Certificate of Confidentiality if reasonable and available.

HIPAA

The Health Insurance Portability and Accountability Act of 1996 (HIPAA) final rule was issued 8/14/02 and becomes effective April 14, 2003. Any PI who intends to conduct research involving private health information (PHI) as defined under this law (45 CFR 164.501) must be able to demonstrate compliance with the requirements under 45 CFR 164.508(c)(1-4) and 45 CFR 164.512(i).

For more information, visit this web site or contact the HSB Administrator

Conflict of Interest

[This section was adapted from the Association of American Medical Colleges "Guidelines for Dealing with Faculty Conflicts of Commitment and Conflicts of Interest in Research", which was adopted by their Executive Council on February 22, 1990.]

In research, *conflicts of interest* (COIs) refers to situations in which financial or other personal considerations may (or may appear to) compromise a researcher's professional judgment in conducting or reporting research. Such conflicts may impart bias in collection, analysis, and interpretation of data, as well as the hiring of staff, procurement of materials, sharing of results, choice of protocol, and the use of statistical methods. COIs are particularly important to consider in biomedical and behavioral research because of the potential impact on human health.

It is not possible to completely eradicate the potential for COIs because there are certain rewards that are inherent in the structure of the research enterprise. Such rewards may be completely unrelated to relationships with industry or private sponsorship. For example, positive research results per se may contribute to opportunities for publication, promotion, tenure, grant renewals,

and so forth. In addition, positive results are often more gratifying and lead to greater personal satisfaction than negative outcomes. In a sense, these influences can be as much a source of conflict in the search for truth as interests of a pecuniary nature. But kept in perspective, such incentives are not inherently bad and are indeed the motivating forces for diligent scientists. Such conflicts become detrimental when the potential rewards, financial or otherwise, cause deviation from absolute objectivity in the design, interpretation, and publication of research activities, or in other academic and professional decisions.

The mere appearance of a conflict may be just as serious and potentially damaging as an actual distortion of objectivity. Reports of conflicts based on appearances can undermine public trust in ways that may not be adequately restored even when mitigating facts of a situation are brought to light. Apparent conflicts should be evaluated and managed with the same rigor as known conflicts.

Some potentially problematic situations include:

- Engaging in research when the PI or his or her immediate family has a financial, managerial, or ownership interest in the sponsoring company or in the product under evaluation
- Accepting gratuities or special favors from research sponsors
- Entering into a consultant arrangement with an organization or individual having an economic interest in related research

PIs are required to be familiar with CPR 001.2.3, *Personal Conflicts of Interest/Employee Relationships With Outside Organizations*, and should contact the SNL Legal Division with questions or concerns regarding potential conflicts of interest with their research.

Informed Consent

Informed consent is an ongoing process that starts with the initial presentation of a research activity to a prospective subject and continues until the subject ends his/her participation or the study closes. Typically, potential subjects are unaware of research activities prior to the initial presentation, and many subjects make their decision whether to participate during the initial contact. As a result, the greatest potential for misunderstanding occurs in the initial contact, and prospective subjects should be allowed sufficient time to absorb and reflect on the nature of participation.

The second step in the consent process is presenting the consent form to subjects. A member of the research team should ensure that the subject reads the consent form and asks the subject if he/she understands the information. In situations where the ability of the subject to understand the form is in question, (e.g., the form includes complex scientific information), the researcher may wish to ask questions of the subject to ensure understanding. In assessing the subject's comprehension of the consent form, researchers should request that the subject indicate the risks of participation, how the subject may withdraw, and what alternatives exist to participation in the research.

Potential subjects should have an opportunity to take the consent form home to consult with family or friends if they so desire. If the individual decides to participate, he/she signs the consent form on a return visit. The person obtaining the consent also signs the form at this time, and provides each subject a copy of the signed consent.

Consent does not end with a signature on a form, but is an ongoing process that involves the

constant re-evaluation of current information and procedures. PIs are ethically obligated to keep subjects apprised of all issues related to their participation in the study.

Note: PIs must inform the HSB of any new information provided verbally to subjects and provide the HSB a copy of any new written information.

Federal regulations stipulate eight basic elements of informed consent, and six additional elements that may be added to a consent form when appropriate (see Appendix D, "Elements of Informed Consent"). The consent document must convey all necessary information to the prospective subject in as clear and easily readable a manner as possible.

Special Subject Populations *(also see Appendix F)*

Minors

Involving children (typically considered to be anyone who has not yet reached the age of consent as defined by state law) in research requires the permission of their parents or legally authorized representatives. Children are legally unable to give valid consent because they have not reached their full intellectual and emotional capacities.

Assent: Federal regulations require the written assent of children age 7 or older as well as the written permission of the parent(s). Assent is defined as "an agreement by an individual not competent to give legally valid informed consent (e.g., a child or cognitively impaired person) to participate in research." Mere failure to object should not be construed as assent. The child's assent is required in all research where the subject has the capacity to comprehend aspects of the study, particularly if the research: (1) does not involve interventions likely to benefit them; and (2) the children can comprehend and appreciate what it means to be a volunteer for the benefit of others.

Parental permission: Current regulations avoid the term "consent" when one person grants approval for another to participate in research. Parents or legal guardians therefore grant "permission" for children to participate in research (45 CFR 46.408). The "permission" form is, in essence, a consent document and should follow all applicable requirements for informed consent as outlined in this manual. Investigators should obtain written permission from the parent/guardian prior to contacting children for participation in research.

Non-English Speaking Subjects

To meet the requirements of 21 CFR 50.20, the consent document must be in language understandable to the subject. If a study includes non-English speaking subjects, researchers should consider the use of translators in the consent process and a copy of the translated consent form must be submitted with the review package. The HSB may request that the PI provide some evidence that the translation is accurate.

Subjects Unable to Consent

When a study involves subjects who cannot give consent for themselves (e.g., young children, mentally handicapped persons, unconscious patients) the HSB may waive this requirement if sufficient justification for use of the particular subject group is presented and if appropriate measures for obtaining consent from a legally authorized representative or a relative and/or subject advocate are followed. (For info on unborn fetuses, see Chapter 7.)

Waiver of Informed Consent

Since written informed consent is essential to the protection of human subjects, federal regulations allow the HSB to waive the requirements only under special conditions. As a result, waiver of informed consent is easily misunderstood and it is often unclear whether a PI is requesting a waiver of documentation of informed consent or a waiver to all or part of the consent process. If you have any questions or concerns regarding a waiver of informed consent, contact the HSB Administrator.

The HSB may only grant a waiver of or amendment to the informed consent process by a vote of the full Board. Therefore, the HSB may not approve a request for waiver or modification of the informed consent during expedited review.

Waiver of Consent Documentation

Federal regulations allow the HSB to waive the requirement for the investigator to obtain a signed consent form if it finds that: [10 CFR 745.117 (c)]

- the only record linking the subject and the research would be the consent document, and the principal risk would be potential harm resulting from a breach of confidentiality; **or**
- the research presents no more than minimal risk of harm to subjects and involves no procedures for which written consent is normally required outside of the research context.

Note: If an investigator does request a waiver of signed consent, then the application must provide a written justification for doing so.

Federal regulations stipulate that, "in cases where the documentation requirement is waived, the IRB may require the investigator to provide subjects with a written statement regarding the research." The HSB requires a written information sheet that includes most or all of the same elements as a consent form, but does not require the signature of the subject.

Waiver or Alteration of Informed Consent

The HSB may approve a consent procedure that omits or alters some (or all) elements of informed consent, or it may waive the requirement to document informed consent, provided one of the following sets of conditions exists and is documented: [10 CFR 745.116 (c)]

1. The research or demonstration project is conducted by or subject to the approval of state or local government officials and is designed to study, evaluate, or otherwise examine (a) programs under the Social Security Act, or other public benefit or service programs; (b) procedures for obtaining benefits or services under those programs; (c) possible changes in or alternative to those programs or procedures; or possible changes in methods or levels of payment for benefits or services under those programs; and (d) the research could not practicably be carried out without the waiver or alteration.
2. The research meets all of the following conditions: (a) the research involves no more than minimal risk to the subjects; (b) the waiver or alteration will not adversely affect the rights and welfare of the subjects; and (c) the research could not practicably be carried out without the waiver or alteration, and whenever appropriate, the subjects will be provided with additional pertinent information after participation.

Note: Federal regulations **do not** allow a waiver of the conditions of informed consent

because the conditions are difficult or because they make it difficult to enroll subjects in the research.

Use of Non-SNL Consent Form

When a SNL researcher conducts research that will be carried out only at another study site, that site's IRB may have different standards for consent documentation. The HSB will consider a request to approve use of the other IRB's approved consent form in such cases, as long as it satisfies the federal requirements for informed consent. Collaborators should note SNL's involvement in the study (typically, under the description of purpose or background).

Deception or Withholding Information

The intent of informed consent is comprehensive, honest, and understandable disclosure of all elements of the subject's participation in research. However, some research plans call for PIs to withhold information about the real purpose of the study or to intentionally give subjects false information about some aspect of the research. As a result, subjects cannot give fully informed consent prospectively. Minor deception, such as withholding specific points of interest in an attempt to prevent a bias in the results, can be acceptable, provided that the subject is fully debriefed after participation. Risks stemming from major deception, such as leading a subject to believe that s/he has committed a crime or has a disease, are more problematic and must be clearly counterbalanced by the benefits of the research.

Note: Incomplete disclosure or deception **cannot** be used to secure the participation of subjects in research. The HSB will not approve research that entails more than minimal risk and withholds information that is material to the subject's decision to participate in the study.

For the HSB to adequately review the research, investigators must justify, in the protocol, the reasons for deceiving or withholding information from subjects, including an explanation of:

- the necessity for deceiving subjects,
- how the potential benefits of the research justify the use of deception, and
- how the investigators will conduct the debriefing.

In addition, investigators must include a debriefing script or a copy of the exact information that subjects will receive regarding their participation in the research.

7.0 Special Research Issues

This chapter discusses special issues regarding human subject research.

Collaborative Projects

When conducting cooperative research projects that involve SNL and one or more other institutions, SNL and the other institution(s) shall each be responsible for safeguarding the rights and welfare of human subjects. SNL may enter into a joint review arrangement, may rely upon the review of the cooperating institution's qualified Institutional Review Board (IRB), or may make similar arrangements to avoid duplication of effort in accordance with federal regulations.

Classified Projects

Classified or sensitive projects may** require Full Board review at a convened meeting. If no

classified or sensitive information is relevant to the protection of human subjects, and the research can be accurately and comprehensively described to members of the HSB who do not hold security clearances, then the review can be conducted in an unsecured environment. If these conditions cannot be met, then the review must be conducted in a secure environment, and each member present must have the appropriate security clearance. A majority of HSB members, including at least one non-scientist, must be present at this secure review.

**a recent change in DOE guidance on classified research has resulted in a substantive change in SNL policy in this area. Previously, all classified research required Full Board review to meet the intent of the 1997 Presidential Memo on classified research. Now, classified research may qualify for exempt or expedited review according to the same requirements that apply to all non-classified human subject research.

International Projects

Note: Human subjects research involving a foreign component can be very complex. PIs should contact the HSB Administrator as early as possible for assistance.

Research on human subjects must adequately protect the rights and welfare of the subjects **regardless of where that research is conducted**. All human subjects research that would be subject to US federal regulations if conducted wholly within the United States, must comply with the federal regulations. Currently, no international code prescribes exactly the same procedures for protecting human subjects, as do the US regulations. However, the procedures of a foreign country may be substituted for those required by the federal regulations if approved by the DOE Office of Science.

PIs working on projects outside of the United States that employ human subjects must obtain all approvals necessary for domestic research. The PI must also assure the HSB that an established IRB, fully constituted in the geographic vicinity of the actual work, has reviewed and approved the entire effort. This frequently necessitates that:

- The foreign institution convenes an IRB with members selected according to the US federal guidelines.
- The instructions to the IRB members are translated from English into the appropriate language.
- The protocol and informed consent documents are written in the appropriate language and translated into English.
- Minutes of the meeting including approval are translated into English and forwarded to the HSB.
- All the documents employed by the local IRB with translations in English must be part of the submission to the HSB.
- PIs must be knowledgeable and sensitive to issues such as the expectations of the local volunteer population, the practices of the local collaborating experimenter(s), the meaning of informed consent, and possible coercion and enticement activities.

Projects Involving Toxic or Potentially Harmful Agents

Using human subjects in research that involves exposure to potentially toxic materials or potentially harmful physical agents (e.g., lasers, electromagnetic radiation, noise, heat, etc.) requires careful consideration. To allow the HSB to fully evaluate the risks and benefits of the

proposed work, PIs must submit information documenting the expected exposure of subjects to these agents, and must have their dose calculations independently reviewed and validated. Any qualified independent party, within or outside SNL can perform this review, and the PI is responsible for any cost associated with such validation.

The documentation should provide enough information for the HSB to assess the adequacy of the independent validation and must include the following:

- The assumptions used regarding subjects, agent(s) and quantity, route of exposure, and frequency or duration of exposure.
- The calculations that yield the estimated dose, and, whenever possible, quantitative risk associated with the exposure.
- Reference to any applicable community or occupational standards.
- A statement that the reviewer has no direct involvement in the research.
- A brief (2- to 4-sentence) summary of the qualifications of the reviewer.

If the proposed subjects are employees at SNL or a collaborating institution, and the proposed exposure is to chemical agents involving inhalation only, and for which there is an existing OSHA Permissible Exposure Limit (PEL) or American Conference of Governmental Industrial Hygienists Threshold Limit Value (TLV), the analysis may be based on exposure rather than absorbed dose.

Medical Devices and Research Regulated by the FDA

See Appendix E, "FDA-Regulated Studies," for information on medical devices.

Vulnerable Populations

See Chapter 6 for special informed consent issues of vulnerable populations.

See Appendix F, "Additional Protections for Vulnerable Populations," for information on research involving children, pregnant women, fetuses, and prisoners.

Co-workers as Subjects

The people you work with may not appear very susceptible to undue influence. Yet, all SNL personnel (employees, contractors, and students) are vulnerable to perceived, even if unintended, pressures to appear cooperative and supportive of projects conducted by their supervisor and co-workers. The following suggestions may reduce the possibility of unintended coercion, while still permitting these individuals to participate as subjects in research:

- Posting HSB-approved advertisements throughout the site to recruit subjects from a broad base of employees, contractors, and students
- Avoiding any personal solicitations of co-workers by investigators, or fellow co-workers

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8.0 AFTER APPROVAL – CONDUCTING HUMAN SUBJECTS RESEARCH

Before beginning a ***research*** protocol, the ***Principal Investigator (PI)*** must be able to show that:

- The proposed research and consent documents have been approved by the HSB.
- A copy of this manual (or the url) has been given to each member of the research team, with the notice that s/he is accountable for knowing his or her responsibilities.
- All subjects will be fully informed and their consent documented in signed consent forms (unless the signature requirement was specifically waived by HSB) before they participate in research activities

Reporting Requirements

Once the study begins, the PI has several reporting responsibilities. See the Reporting Table for Research Involving Human Subjects (Appendix I) to learn who must report what to whom and when.

Situations that indicate "immediate" or "prompt" reporting, must be done via phone or in person to the HSB Administrator, and followed up with a written description via e-mail within 2 days. All other reporting must be done in writing within the timeframe allowed.

All non-exempt research approved by the HSB must be re-reviewed annually. The due date is indicated on the Notice of Approval. When a study is finished, a Completion/Termination Request (FR-MED129) must be filled out and returned to the HSB Administrator along with a summary report describing what the results of the study were.

Adverse Events 🕮

The PI must immediately report to the HSB all **adverse events**, even if there is no obvious relationship between the study activities and the event. The HSB, in turn, evaluates and reports all adverse events to SNL management, to DOE, to OHRP, and to any other federal agency funding the research protocol.

The PI must assess the adverse event and its relationship to the study, and then report the findings within 5 days directly to the HSB Administrator (MS-1015, treser@sandia.gov).

It is the responsibility of the investigator to ensure that written notification of adverse events are submitted to OPRS. The principal investigator must complete, with his/her original signature, an Adverse Event Report and attach any additional information necessary in evaluating the report (i.e. medical report).

The IRB relies upon the expertise of the UNLV primary investigator to assess the report. The adverse event report form will require the principal investigator to assess the causality of the event, the seriousness of the event, and whether or not the event was expected and/or related. In addition, the IRB will seek input from the investigators as to if the risk/benefit ratio has been effected due to the adverse event.

In reviewing the adverse event, the HSB will consider whether it affects the risk/benefit ratio to ensure adequate protection of the welfare of subjects. In consultation with the investigator, and as result of the HSB review process, the IRB may:

- Reconsider approval of the study
- Require the investigator to modify the protocol to minimize risks to subjects
- Revise protocol to reflect the risks to subjects

- Require subjects be re-consented
- Require no additional action on the part of the PI

Report Content

PIs must include the following information when reporting any incident, experience, or outcome to the IRB:

- title of the research protocol, investigator's name, and the HSB tracking number
- a detailed description of the adverse event, incident, experience, or outcome;
- a description of any changes to the protocol or other corrective actions that have been taken or are proposed in response to the unanticipated problem.

A problem that meets these criteria generally will warrant consideration of substantive changes in the research protocol or informed consent process/document or other corrective actions in order to protect the safety, welfare, or rights of subjects or others.

When an adverse event rises to the level of an unanticipated problem, the PI must also include in the report a clear explanation of why the adverse event has been determined to be an unanticipated problem.

An **adverse event** is defined as any undesirable effect, whether expected or unexpected, that results from or is indirectly related to the entire research process (e.g., mishaps, mistakes, incorrect dosage administered, reconsideration of human subject involvement.).

Verification of Information

The HSB will determine whether a study requires verification from sources other than the PI to ensure that no unapproved changes have occurred since the previous HSB review. Such verification may include:

- Conducting audits or inquiries to collect information,
- Observing or having a designee observe the informed consent process and conduct of the research, and/or
- Examining contents of manuscripts or reports resulting from protocol activities.

The HSB will seek verification from sources other than the PI that no material changes have occurred since previous IRB review when:

- The HSB doubts the veracity of the information provided by the PI.
- The information provided by the PI is inconsistent with other information and the inconsistency cannot be resolved through discussion with the PI.
- The PI has been found to be in serious or continuing noncompliance in the previous 3 years.
- The HSB determines that verification from sources other than the PI is prudent.

Research Conduct

During the course of the research, the PI must comply with all HSB decisions and conditions and the responsibilities described in this manual. In addition, Sandia expects its researchers to adhere to the federal Policy on Research Misconduct (available online at http://www.ostp.gov/html/001207_3.html) as well as SNL policy specified in CPR001.2.1, *Setting the Standard: Code of Ethics and Business Conduct*, and CPR001.2.3, *Personal Conflicts of Interest/Employee Relationships with Outside Organizations*.

Note: The HSB may contact subjects directly or monitor the research to evaluate the PI's conduct and compliance with requirements.

9.0 MONITORING

The ***Principal Investigator (PI)*** may conduct any activities in a protocol approved by the HSB. However, no deviations from an approved protocol are permitted without prior written HSB approval, except when such deviation is necessary to eliminate an immediate hazard to a study subject. Federal regulations authorize the HSB to monitor human subject research to ensure that protection of human subjects is implemented and enforced. Continuing review (see Chapter 5) is one monitoring tool. Another is to have the HSB or a third-party observe the research (see Appendix H, "Criteria for Determining Additional Monitoring"). This Chapter discusses what is expected of a PI while conducting human subject research, and what consequences are likely if those expectations are not met.

To establish whether a situation is serious, the HSB considers each of the following:

- potential risk to subjects
- severity of violation to the process
- a pattern of repeated minor violations
- intent

Temporary hold means discontinuation of previously approved research, directed by the IRB, pending further investigation of alleged instances of noncompliance and/or implementation of minor corrective action

Suspension means discontinuation of previously approved research, directed by the IRB, following determination of instances of serious noncompliance, and pending formulation and implementation of substantial corrective action.

Termination means closure of previously approved research, directed by the IRB, following determination of instances of serious noncompliance for which implementation of corrective action is not appropriate.

Noncompliance/Violations/Complaints 🕮

When the actual activities being performed in a study vary from what was reviewed and approved by the HSB, the study is not in compliance with the HSB approval. Reports of such a variance may come from a variety of sources: research subjects, HSB members, research staff, or

people not connected with the research.

Anyone who suspects a problem with any study involving human subjects should report it to the HSB at 845-9171. All reports of non-compliance, alleged violations of ***human subject*** regulations, and complaints from research subjects will be investigated by the HSB. Allegations that are substantiated will be forwarded to the HSB Chair for appropriate action.

The HSB Chair will promptly report the following to the institutional official and to DOE:

- any unanticipated injuries or problems involving risks to subjects or others
- any serious or continuing noncompliance with the regulations or requirements of the HSB
- any suspension or termination of HSB approval for research

Deviation from Approved Protocol 🕮

Any individual noting a deviation from an approved protocol should report the deviation or concern to the HSB. The HSB will then review the protocol and relevant documentation, and assess the deviation according to two main criteria:

- potential or actual harm to the subject
- potential or actual effect on the integrity of the study data

The HSB will determine whether the violation is serious (a subject was harmed, the potential for harm was created, or the violation compromised the integrity of the study) or non-serious (violation did not harm or potentially harm a subject and does not compromise study integrity).

The HSB will also determine whether further corrective action is warranted:

- If the protocol violation is deemed serious, the HSB will suspend the study.
- If the protocol violation is deemed non-serious, a memo will be sent from the HSB Chair to the PI's manager.

If the HSB finds a pattern of protocol violations by a particular PI with no evidence of effective corrective action by the PI's manager, the HSB will suspend all protocols for which the individual is the PI and request the PI's manager to conduct a root cause investigation.

All findings and conclusion of the HSB will be documented in the protocol file.

Suspension/Termination 🕮

The HSB has both the authority and the responsibility to suspend or terminate any research involving human subjects that is not being conducted in accordance with the HSB requirements or that has been associated with any unexpected serious harm to subjects. Any such suspension or termination of approval must be reported promptly to the PI, and shall include a statement of the reasons for the suspension. The HSB Chair must also notify the SNL Executive Vice President, the director who approved the project, DOE, and, if applicable, OHRP.

If a PI **fails to submit** a completed Request for Continuing Approval form prior to the HSB Approval expiration date, the HSB Administrator will contact the PI and his/her manager to inform them that the PI is no longer authorized to continue the study.

Note: The HSB makes every effort to avoid suspension of an otherwise active protocol and to prevent studies from being conducted beyond the approval period.

A **suspended study** may be re-opened after the problem triggering the suspension has been resolved. A **terminated study** may not be reopened.

HSB Suspension/Termination Procedure 🕮	
Step	**Action**
1.	The HSB Chair notifies the HSB Administrator, the PI, the PI's manager, and the director who approved the project of his/her decision.
2.	The HSB Administrator: a. Prepares a letter to DOE and OHRP (if applicable) to report the action. b. Sends form FDA 3500(6/83) to the FDA to report the action. c. Notifies the sponsor of the research of the action.
3.	The full HSB reviews the suspension or termination as soon as possible.

Self-Assessment

The HSB shall periodically conduct self-assessments to ensure compliance with requirements and to evaluate the effectiveness/efficiency/suitability of procedures. Such assessments are typically conducted by the HSB Administrator, but may be conducted by other members appointed by the HSB Chair.

10.0 MEETINGS

Convened Meetings

Convened meetings of the full HSB are typically held quarterly in January, April, July, and October (first month in each quarter of the fiscal year). However, the board may be called into a meeting by the Chair at the request of any HSB member, SNL official, or the HSB Administrator to address any concern about the rights and welfare of any subject. A PI may request to attend a meeting to discuss his/her protocol; however, no PI may be present during a vote on his/her protocol. Attendance is restricted to board members and invited guests.

Physical presence at convened meetings is expected unless a member lives outside New Mexico or is unable to attend in person. In those instances, those members may participate via telephone or video conferencing as long as each member (a) has received all pertinent material prior to the meeting, and (b) can actively and equally participate in the discussion of all protocols. Minutes should clearly document that these conditions are met. When they are, those participating via telephone or video link may be counted in the quorum.

The HSB periodically meets in smaller groups to review proposed studies eligible for expedited review. Such meetings are not considered convened meetings.

Agendas

The HSB Administrator prepares a preliminary agenda for each meeting, and, after approval by

the HSB Chair, e-mails the agenda to all members at least one week prior to the meeting. A final agenda is distributed at each meeting.

Minutes 🕮

The HSB Administrator records the minutes of each convened meeting of the HSB (see "Record Keeping" for required content of minutes). Upon review and approval by the HSB Chair, the Administrator distributes meeting minutes to the membership for review and comment as soon as possible after a meeting. The board approves minutes at the next full meeting.

Voting

Quorum

A quorum is defined as a simple majority of HSB voting members, including at least one non-scientist member. When a protocol will be reviewed at a meeting, the Administrator polls members before the meeting to assure a quorum; however all HSB members are encouraged to participate at all HSB meetings.

Research can only be approved by a majority vote of this quorum. Should the quorum fail during a meeting (i.e., loss of a majority through recusal of members with conflicting interests or early departures, or absence of a non-scientist member), the HSB may not take further actions or votes unless the quorum can be restored.

Eligible Votes

All voting is conducted in closed session, and voting privileges shall be limited to HSB members present at the meeting or participating via phone, provided that they have received all necessary information prior to the vote and have been able to participate fully and completely in the pre-vote discussion. Proxy votes are not accepted, and a separate vote is required for each protocol under review. Member votes are recorded by the Administrator via a show of hands, and a majority vote is required for any HSB determination.

Abstentions

No member may vote or participate in the review of any protocol in which s/he has a conflicting interest, except to provide information requested by the HSB. It is the member's responsibility to inform the board that there is a conflict. An HSB member may also abstain from voting for reasons other than a conflict of interest. The meeting minutes should record the abstention as (a) due to conflict, (b) due to some other stated reason, or (c) reason not specified.

11.0 KEEPING RECORDS

Records Retention and Access

All records related to SNL ***human subject research*** shall be retained indefinitely and shall be accessible for inspection and copying by authorized representatives of the department or agency at reasonable times and in a reasonable manner. Do not destroy until an approved retention period has been authorized. [Note: current retention period is: Destroy 75 years after termination or completion of study, *SNL Record Retention and Disposition Schedul*e (Record Series # HR-102-209-000)]

HSB Records

All official HSB records are stored in the HSB Administrator's office in locked file cabinets for a minimum of three years after completion of the study. After that time, all HSB records will be archived and retained according to the *SNL Record Retention and Disposition Schedul*e in effect at that time.

Protocol Records 🕮

The HSB Administrator assigns each protocol a unique, chronological number that indicates the fiscal year and order it was received. Official HSB records for each protocol include the following:

- all documentation reviewed by the HSB
- all correspondence related to the protocol
- copies of any press releases or media coverage of the protocol
- copies of any minutes of HSB meetings involving that protocol
- notes from protocol review sessions
- approved consent forms, which must include the initial approval date, the current approval date, the expiration date and the corresponding protocol number. (Note: The PI retains all **signed** consent forms.)
- all other documents specifically approved by the HSB relating to the protocol, (e.g., any subject recruitment material).
- progress reports submitted by the PI, reports of injuries to subjects, and statements of significant new findings provided to subjects
- records of continuing review activities.

Meeting Minutes and Agendas 🕮

Minutes of HSB meetings shall be taken in sufficient detail to show the following:

- attendance, including members (and any guests) present, as well as late arrivals or early departures by members
- actions taken by the HSB (including listings of expedited reviews and annual reports) and deliberations, which are recorded without attribution
- the vote on these actions, including the number of members voting for, against, and abstaining (also recorded without attribution)
- the basis for requiring changes in or disapproving research
- the basis for requiring an approval period shorter than one year
- a written summary of the discussion of controverted issues and their resolution
- reports of unanticipated problems and adverse effects.

Each protocol discussed shall indicate the HSB protocol number and title, and copies of any handouts distributed during the meeting will be attached to the minutes. Minutes are filed chronologically. In addition, non-protocol specific correspondence is kept in a separate file.

Minutes are distributed to members for review as soon as possible after a meeting. Any corrections/comments to the minutes are noted in the minutes of the next meeting, and a vote is

taken to approve the minutes.

Training Records 🕮

The HSB Administrator retains copies of all training material distributed to members, as well as records of all local seminars and conferences attended by any HSB member, and training records from CITI. Members are encouraged to send copies of any completion certificates from online tutorials or other training sessions to the Administrator.

PI Records

The PI must retain all research related records, including original, signed and witnessed consent forms, that originate with the PI or the research team, for a minimum of three years after completion of the study. After three (3) years, these records may be archived, but may not be destroyed until 75 years after completion of the study [*SNL Record Retention and Disposition Schedul*e (Record Series # HR-102-212-000)]. The PI is responsible for his or her clear understanding of the retention requirements of SNL and their sponsor.

All documents, electronic files, videotapes, etc., that contain the subject's personal identifiers must be kept in locked storage or access-controlled databases, with access restricted to the PI and members of the research team. All PI records must be accessible for inspection and copying by the HSB or authorized representatives of DOE or DHHS at reasonable times and in a reasonable manner. Access restrictions must continue in force until the records are destroyed.

Archiving Records 🕮

Any human subject records sent to SNL records storage after three years must clearly identify any special handling requirements. For example, the records transmittal form should indicate:

> "These human subject research records are under a DOE moratorium on destruction [*SNL Record Retention and Disposition Schedul*e, (Record Series # HR-102-212-000]. These records must not be destroyed for 75 years after completion of the study, which occurred on _____."

If the records require restricted access, attach a memo or other appropriate paperwork identifying which specific individuals are authorized access to the records. If the records reveal the identity of the individual subjects, access should be limited to the original research team. If none of the research team are still employed at SNL, access must be approved by the HSB Chair.

Close Out Records 🕮

To formally complete or terminate a study file, the PI must submit a Completion/Termination Request (FR-MED129). As part of the closeout process, PIs must also submit a 1-2 paragraph summary of study results.

12.0 REFERENCES

Regulatory

10 CFR 745, *Protection of Human Subjects*. ["Common Rule," DOE]

21 CFR 50, *Protection of Human Subjects*. [Informed Consent, FDA]

21 CFR 54, *Financial Disclosure by Clinical Investigators*. [FDA]

21 CFR 56, *Institutional Review Boards*. [FDA]

21 CFR 812, *Investigational Device Exemptions*. [FDA]

45 CFR 46, *Protection of Human Subjects*. [additional protection for vulnerable subjects, HHS]

DOE O 443.1, *Protection of Human Subjects*.

DOE P 443.1, *Protection of Human Subjects*.

National Research Act (Public Law 93-348).

Implementation

DOE, *Protecting Human Research Subjects Guidebook*.

OHRP, FWA00003764, *US Department of Health and Human Services Federal Wide Assurance (FWA) for the Protection of Human Subjects for Domestic Institutions*.

SNL, CPR300.5.2, *Protection of Human Research Subjects*.

SNL, HSB web site internal

SNL, HSB web site external

Related

Belmont Report

SNL, CPR001.2.1, *Setting the Standard: Code of Ethics and Business Conduct*.

SNL, CPR 001.2.3, *Personal Conflicts of Interest/Employee Relationships With Outside Organizations*.

13.0 REVISION RECORD

Issue	Page(s)	Date	Authorized by	Changes
A	All	10/16/01	T. Reser	Create new document
B	All	5/16/03	T. Reser	Revise following reviews by full board and PI, and benchmarking
C	All	4/14/05	T. Reser	Delete all forms, update training instructions
	8-9, 17	10/4/05	T. Reser	Clarify responsibilities and Step 3.
D	All	6/1/08	T. Reser	Review, update, and clarify as needed

14.0 DEFINITIONS

Adverse event - An undesirable effect, whether expected or unexpected, that results from or is indirectly related to the entire research process (e.g., mishaps, mistakes, incorrect dosage administered, reconsideration of human subject involvement.). All adverse events must be reported to the HSB even if there is no obvious causal relationship between the protocol procedures and the event.

DOE – For purposes of this document, "DOE" refers to the Human Subjects Research Program Manager in the Office of Science, Washington, DC

DOE Human Subjects Research Database - A compilation of summary information on non-classified, non-exempt DOE research, which is available on the DOE HSRD website and updated annually.

Federalwide Assurance (FWA) - A written commitment from an institution to the Office for Human Research Protections (OHRP) that ensures institutional compliance with all pertinent federal regulations for the protection of human research subjects. Every institution engaged in human subjects research supported or conducted by the Department of Health and Human Services (DHHS) must obtain an FWA.

HSB - Sandia's Human Studies Board, the Institutional Review Board (IRB) established in accordance with and for the purposes expressed in 10 CFR 745.

Human subject - A living individual about whom an investigator conducting research obtains:

- Data through intervention or interaction with the individual, or
- Identifiable private information or materials.

Informed consent - The knowing consent of the human research subject, or the subject's legally authorized representative, so situated as to be able to exercise free power of choice without undue inducement or any element of force, fraud, deceit, duress, or any other form of constraint or coercion.

Institutional Review Board (IRB) – The generic term used in all regulations for the local body that reviews and approves human subject research. At SNL, this body is known as the Human Studies Board (HSB).

Legally authorized representative - An individual or judicial or other body authorized under applicable law to consent on behalf of a prospective subject to the subject's participation in the procedure(s) involved in the research.

Minimal risk – A risk is considered minimal if the probability and magnitude of harm or discomfort anticipated in the research are not greater in and of themselves than those ordinarily encountered in daily life or during the performance of routine physical or psychological examinations or tests.

Minor – Anyone who has not yet reached the age of consent as defined by state law. This currently ranges from 14 to 18 in the US, and as low as age 12 in other countries.

Principal Investigator (PI) - The scientist or other individual designated by SNL who is responsible for the scientific or technical direction of the project.

Private information - This includes information about behavior that occurs in a context in which an individual can reasonably expect that no observation or recording is taking place, and information that has been provided for specific purposes by an individual and that the individual can reasonable expect will not be made public (e.g., a medical record). Such information must be individually identifiable (i.e., the identity of the subject is or may readily be ascertained by the investigator or associated with the information) in order for obtaining the information to constitute research involving human subjects.

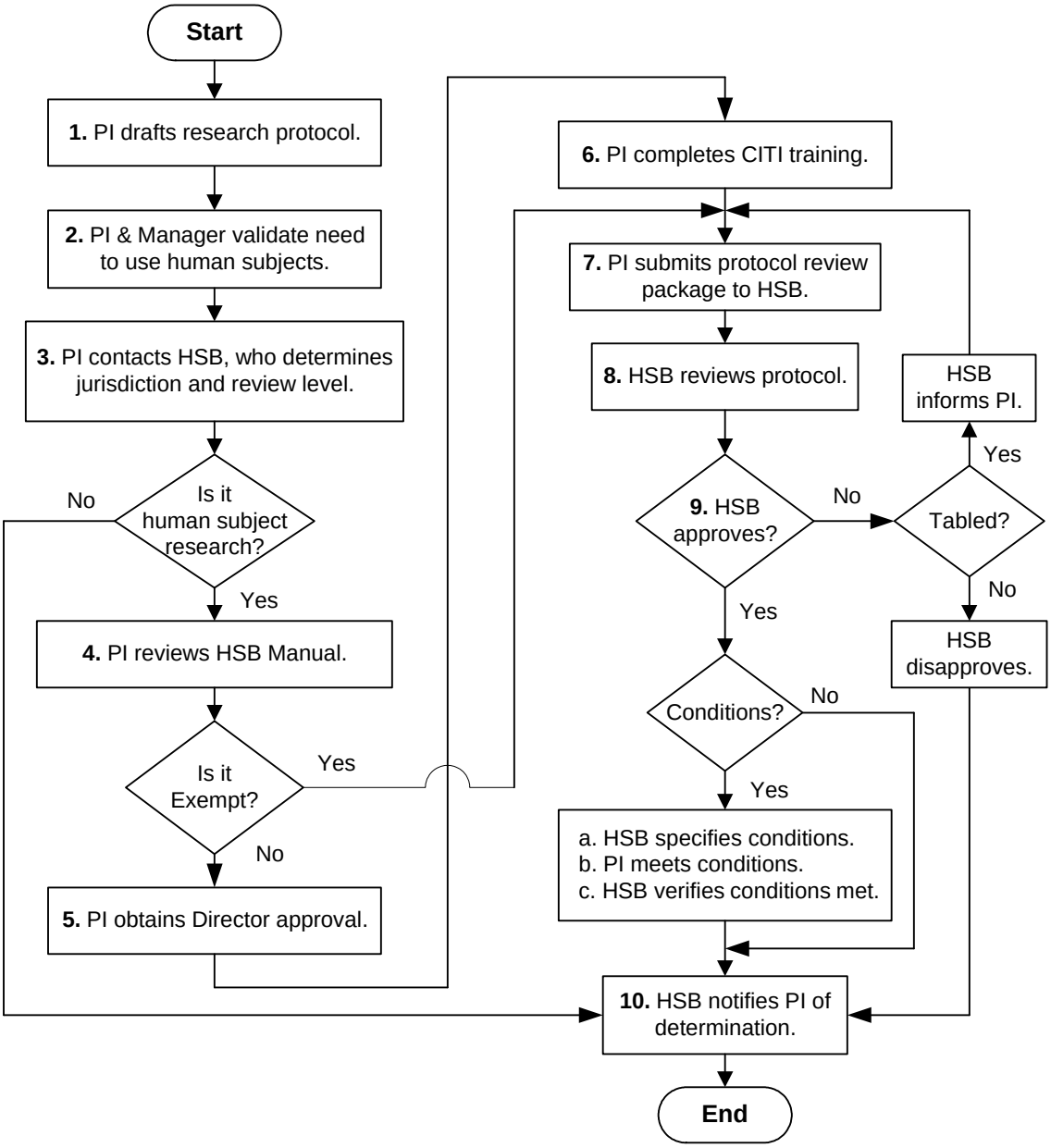
Protocol review package – The minimal information required by the HSB of the PI in order to conduct a review of proposed research. See Step 7 in Chapter for a complete list of what this package includes.

Research - A systematic investigation, including research development, testing and evaluation, designed to develop or contribute to *generalizable* knowledge. Activities that meet this definition constitute research for purposes of this document, whether or not they are conducted or supported under a program that is considered research for other purposes.


Terry Reser, treser@sandia.gov

Appendix A

HSB Initial Review/Approval Process Flow Chart



HSB - Human Studies Board
PI - Principal Investigator

Appendix B

Exempt Research Activities

[10 CFR 745.101(b)]

Unless otherwise required by federal department or agency heads, research activities in which the only involvement of human subjects will be in one or more of the following categories are exempt from HSB review:

(1) Research conducted in established or commonly accepted educational settings, involving normal educational practices, such as (i) research on regular and special education instructional strategies, or (ii) research on the effectiveness of or the comparison among instructional techniques, curricula, or classroom management methods.

(2) Research involving the use of educational tests (cognitive, diagnostic, aptitude, achievement), survey procedures, interview procedures or observation of public behavior, unless:

(i) Information obtained is recorded in such a manner that human subjects can be identified, directly or through identifiers linked to the subjects; ***and***

(ii) any disclosure of the human subjects' responses outside the research could reasonably place the subjects at risk of criminal or civil liability or be damaging to the subjects' financial standing, employability, or reputation.

(3) Research involving the use of educational tests (cognitive, diagnostic, aptitude, achievement), survey procedures, interview procedures, or observation of public behavior that is not exempt under paragraph (2) above, if:

(i) The human subjects are elected or appointed public officials or candidates for public office; or

(ii) federal statute(s) require(s) without exception that the confidentiality of the personally identifiable information will be maintained throughout the research and thereafter.

(4) Research, involving the collection or study of existing data*, documents, records, pathological specimens, or diagnostic specimens, if these sources are publicly available or if the information is recorded by the investigator in such a manner that subjects cannot be identified*, directly or through identifiers linked to the subjects.

(5) Research and demonstration projects which are conducted by or subject to the approval of department or agency heads, and which are designed to study, evaluate, or otherwise examine:

(i) Public benefit or service programs;

(ii) Procedures for obtaining benefits or services under those programs;

(iii) Possible changes in or alternatives to those programs or procedures; or

(iv) Possible changes in methods or levels of payment for benefits or services under those programs.

(6) Taste and food quality evaluation and consumer acceptance studies, (i) if wholesome foods without additives are consumed or (ii) if a food is consumed that contains a food ingredient at or below the level and for a use found to be safe, or agricultural chemical or environmental contaminant at or below the level found to be safe, by the Food and Drug Administration or approved by the Environmental Protection Agency or the Food Safety and Inspection Service of the U.S. Department of Agriculture.

Note: At SNL, human subject **research that involves human genetic material does not qualify as exempt** and must receive Expedited or Full Board review by the HSB.

***Existing Data**

The term "existing" refers to the time period that the data or material was obtained. Existing material or tissue must be "archived" or "on the shelf" prior to HSB review of the research. If the data/specimens are collected after submitting a protocol to the HSB, the data are not pre-existing and the protocol will require HSB review.

Specimens received as extra material or extra specimens requested from a physician conducting a clinical procedure are not pre-existing or "archived" and thus require written informed consent from the subject and review by the HSB. If there is a link to the patient's identity and a possibility that the patient may be contacted in the future, or a possibility that the research may result in commercial or economic value, an informed consent document is required.

***Subjects Cannot Be Identified (Anonymous)**

Information is considered to be anonymous when there is no possible way to identify the participants from the data collected. Information is not anonymous if anyone, or any procedure (such as accessing a computer database) will identify the subject. In most projects, omitting name and other specific identifiers such as social security number or patient number, is sufficient to qualify a study as anonymous. Sometimes an investigator may preserve a subject's anonymity while still retaining data on individual characteristics such as age, gender, ethnic origin, occupation, or diagnosis. Anonymity is possible only when studying large samples or populations. When the number of potential participants is small and/or the research setting is identified, anonymity can be threatened or compromised even when identifiers have been removed from the data.

Archived pathology or diagnostic specimens that are considered residual biological material and are destined to be destroyed can be used in research and are considered exempt from HSB review if there are **no** patient identifiers linked to the specimen and if the data are not intended to be used in the diagnosis or treatment of a patient. If either of these conditions apply, consent of the research subject is required and the study will require HSB review.

Appendix C

Expedited Review Categories

From Federal Register 11/9/98

Research activities that present no more than minimal risk to human subjects and involve only procedures listed in one or more of the following categories may be reviewed by the HSB through the expedited review procedure. The categories in this list apply regardless of the age of subjects, except as noted.

(1) Clinical studies of drugs and medical devices only when condition (a) or (b) is met.

(a) Research on drugs for which an investigational new drug application (21 CFR 312) is not required. (Note: Research on marketed drugs that significantly increases the risks or decreases the acceptability of the risks associated with the use of the product is not eligible for expedited review.)

(b) Research on medical devices for which (i) an investigational device exemption application (21 CFR 812) is not required; or (ii) the medical device is cleared/approved for marketing and the medical device is being used in accordance with its cleared/approved labeling.

(2) Collection of blood samples by finger stick, heel stick, ear stick, or venipuncture as follows:

(a) from healthy, non-pregnant adults who weigh at least 110 pounds. For these subjects, the amounts drawn may not exceed 550 ml in an 8 week period and collection may not occur more frequently than 2 times per week; or

(b) from other adults and children, considering the age, weight, and health of the subjects, the collection procedure, the amount of blood to be collected, and the frequency with which it will be collected. For these subjects, the amount drawn may not exceed the lesser of 50 ml or 3 ml per kg in an 8 week period and collection may not occur more frequently than 2 times per week.

(3) Prospective collection of biological specimens for research purposes by noninvasive means.

Examples: (a) Hair and nail clippings in a non-disfiguring manner; (b) deciduous teeth at time of exfoliation or if routine patient care indicates a need for extraction; (c) permanent teeth if routine patient care indicates a need for extraction; (d) excreta and external secretions (including sweat); (e) uncannulated saliva collected either in an unstimulated fashion or stimulated by chewing gumbase or wax or by applying a dilute citric solution to the tongue; (f) placenta removed at delivery; (g) amniotic fluid obtained at the time of rupture of the membrane prior to or during labor; (h) supra- and subgingival dental plaque and calculus, provided the collection procedure is not more invasive than routine prophylactic scaling of the teeth and the process is accomplished in accordance with accepted prophylactic techniques; (i) mucosal and skin cells collected by buccal scraping or swab, skin swab, or mouth washings; (j) sputum collected after saline mist nebulization.

(4) Collection of data through noninvasive procedures (not involving general anesthesia or sedation) routinely employed in clinical practice, excluding procedures involving x-rays or microwaves. Where medical devices are employed, they must be cleared/approved for marketing. (Studies intended to evaluate the safety and effectiveness of the medical device are not generally eligible for expedited review, including studies of cleared medical devices for new indications.)

Examples: (a) Physical sensors that are applied either to the surface of the body or at a distance and do not involve input of significant amounts of energy into the subject or an invasion of the subject's privacy; (b) weighing or testing sensory acuity; (c) magnetic resonance imaging; (d)

electrocardiography, electroencephalography, thermography, detection of naturally occurring radioactivity, electroretinography, ultrasound, diagnostic infrared imaging, doppler blood flow, and echocardiography; (e) moderate exercise, muscular strength testing, body composition assessment, and flexibility testing where appropriate given the age, weight, and health of the individual.

(5) Research involving materials (data, documents, records, or specimens) that have been collected or will be collected solely for non-research purposes (such as medical treatment or diagnosis). (Note: Some research in this category may be exempt from the HHS regulations for the protection of human subjects. 45 CFR 46.101(b)(4). This listing refers only to research that is not exempt.)

(6) Collection of data from voice, video, digital, or image recordings made for research purposes.

(7) Research on individual or group characteristics or behavior (including, but not limited to, research on perception, cognition, motivation, identity, language, communication, cultural beliefs or practices, and social behavior) or research employing survey, interview, oral history, focus group, program evaluation, human factors evaluation, or quality assurance methodologies. (Note: Some research in this category may be exempt from the HHS regulations for the protection of human subjects 45 CFR 46.101 (b)(2) and (b)(3). This listing refers only to research that is not exempt.)

(8) Continuing review of research previously approved by the convened IRB as follows:

(a) Where (i) the research is permanently closed to the enrollment of new subjects; (ii) all subjects have completed all research-related interventions; and (iii) the research remains active only for long-term follow-up of subjects; or

(b) Where no subjects have been enrolled and no additional risks have been identified; or

(c) Where the remaining research activities are limited to data analysis.

(9) Continuing review of research, not conducted under an investigational new drug application or investigational device exemption where categories two (2) through eight (8) do not apply but the IRB has determined and documented at a convened meeting that the research involves no greater than minimal risk and no additional risks have been identified.

Expedited review may not be used:

- where identification of subjects and/or their responses would reasonably place them at risk of criminal or civil liability or be damaging to the subjects' financial standing, employability, insurability, reputation, or be stigmatizing, unless reasonable and appropriate protections will be implemented so that risks related to invasion of privacy and breach of confidentiality are no greater than minimal.
- for classified research involving human subjects.

Appendix D

Elements of Informed Consent

Basic Elements of Informed Consent

The researcher shall provide ***all*** of the following information to each subject, in language understandable by the subjects, when seeking informed consent:

a. A statement that the study involves research; an explanation of the purposes of the research and the expected duration of the subject's participation; a description of the procedures to be followed; and identification of any procedures that are experimental.

b. A description of any reasonably foreseeable risks or discomforts to the subject.

c. A description of any benefits to the subject or to others that may reasonably be expected from the research.

d. Disclosure of appropriate alternative procedures or courses of treatment, if any, that might be advantageous to the subject.

e. A statement describing the extent, if any, to which confidentiality of records identifying the subject will be maintained.

f. For research involving more than minimal risk, an explanation as to whether any compensation and/or medical treatment is available if injury occurs and, if so, what they consist of, or where further information may be obtained.

g. An explanation of whom to contact for answers to pertinent questions about the research, about the research subjects' rights, and whom to contact in the event of a research-related injury to the subject.

h. A statement that participation is voluntary, that refusal to participate will involve no penalty or loss of benefits to which the subject is otherwise entitled, and that the subject may discontinue participation at any time without penalty or loss of benefits to which the subject is otherwise entitled.

Additional Elements of Informed Consent

When appropriate, one or more of the following elements of information shall also be provided to each subject:

a. A statement that the particular treatment or procedure may involve risks to the subject (or to the embryo or fetus, if the subject is or may become pregnant) that are currently unforeseeable.

b. Anticipated circumstances under which the subject's participation may be terminated by the investigator without obtaining the subject's consent.

c. Any additional costs to the subject that may result from participation in the research.

d. The consequences of a subject's decision to withdraw from the research, and procedures for orderly termination of participation by the subject.

e. A statement that significant new findings developed during the course of the research that may relate to the subject's willingness to continue participation will be provided to the subject.

f. The approximate number of subjects involved in the study.

g. Any additional information that would meaningfully add to the protection of the rights and welfare of subjects.

Note: These required elements of informed consent are not intended to preempt any applicable federal, state or local laws that require additional information to be disclosed for informed consent to be legally effective.

Appendix E

FDA-Regulated Studies

The Food and Drug Administration (FDA) regulates all human subjects research involving drugs, medical devices, and biologics, including the ingestion or injection of radio-labeled compounds. The FDA requires HSB review and informed consent in much the same way as NIH or DOE; however, FDA has several additional reporting conditions that directly involve investigators.

If a PI is the developer of the drug or device and no commercial manufacturer is involved, then either the PI or the PI's organization may be the sponsor for purposes of designing and organizing clinical trials. The sponsor is responsible for 1) submitting an investigational new drug (IND) or investigational device exemption (IDE) application to FDA and 2) providing a copy of the FDA's response to the IRB. Sponsors also have important administrative and reporting requirements above and beyond those of PIs. SNL employees contemplating the dual role of sponsor-investigator should consult with the HSB Chair or Administrator about these additional responsibilities.

Clinical trials conducted under an IND or IDE issued by FDA must adhere to the protocol as submitted by the investigator. Any modification, such as extension to another age group, use of a different dose, or change in subject eligibility criteria must be approved by both the FDA and the IRB prior to implementation, unless immediate action is required to eliminate apparent immediate hazards to human subjects. Any changes made to eliminate an immediate hazard must be reported to the IRB within five working days.

Note: <u>Deviation from the approved protocol may subject the investigator to sanctions by the FDA and/or the IRB, and possibly also to charges of scientific misconduct.</u>

FDA regulations include specific instructions for the content of records that must be created and maintained in clinical investigations of drugs and devices [21CFR312.62 (drugs) and 21CFR812.40 (devices)]. Contact the HSB Administrator for additional information.

1. Informed Consent Requirements

FDA regulations require written informed consents except in specific emergency conditions. However, California law does not allow for a waiver of written informed consent in emergency situations. Therefore, all FDA-regulated studies conducted in California will require signed consent forms from all participating subjects or their legally authorized representative. New Mexico law has no such provision.

2. Medical Devices

A medical device is defined, in part, as any health care product that does not achieve its primary intended purposes by chemical action or by being metabolized. Medical devices include, among other things, surgical lasers, wheelchairs, sutures, pacemakers, intraocular lenses, and orthopedic pins. Medical devices also include diagnostic aids such as reagents and test kits for *in vitro* diagnosis of disease and other medical conditions such as pregnancy.

Clinical investigations of medical devices must comply with the FDA's informed consent and IRB regulations (21 CFR parts 50 and 56, respectively). Federal requirements governing investigations involving medical devices were enacted as part of the Medical Device Amendments of 1976 and the Safe Medical Devices Act of 1990. These amendments to the Federal Food, Drug, and Cosmetic Act define the regulatory framework for medical device development, testing, approval, and marketing.

Except for certain low-risk devices, each manufacturer who wishes to introduce a new medical device to the market must submit a premarket notification to FDA. FDA reviews these notifications to determine if the new device is "substantially equivalent" to a device that was marketed prior to passage of the Amendments (i.e., a "pre-amendment device"). If the new device is deemed substantially equivalent to a pre-amendments device, it may be marketed immediately and is regulated in the same regulatory class as the pre-amendments device to which it is equivalent. If the new device is deemed not to be substantially equivalent to a pre-amendments device, it must undergo clinical testing and pre-market approval before it can be marketed unless it is reclassified into a lower regulatory class.

a. Device classifications

The FDA is responsible for assuring the safety and effectiveness of medical devices intended for human use, and has classified devices according to their level of risk.

- Class I devices include those devices for which safety and effectiveness can be assured so long as there is compliance with provisions for notification of defects, repair, replacement or refund, records, and reports. Device manufacturers are also required to avoid distribution of adulterated, misbranded, or banned devices.
- Class II devices are those that require something more than proper labeling and quality assurance to ensure their safety and effectiveness.
- **Class III devices** are those that are life-sustaining, life-supporting, implanted in the body, or of substantial importance in preventing impairment.
- 510(K) devices

  When a new device **is substantially equivalent** to one marketed prior to enactment of the Medical Device Amendments (1976), it may be sold without additional proof of safety and efficacy, under Section 510(K) of the federal Food, Drug, and Cosmetic Act. These devices are thus commonly referred to as "510(K)" devices. A sponsor planning to market the device must notify the FDA 90 days in advance of placing the device on the market. If the FDA agrees that the device is substantially equivalent to one already on the market, the device may then be sold without further research. Research activities involving a 510(K) device do not require an IDE, but do require approval by the HSB prior to the initiation of research.

  If the FDA determines that a new device **is not substantially equivalent** to a pre-amendment device, the new device is automatically designated a Class III medical device and the sponsor is required to obtain pre-marketing approval from the FDA. Studies conducted to develop safety and effectiveness data for such devices must be conducted according to the FDA requirements of Investigational Devices [21 CFR 812].

b. Investigational Device Exemptions (IDEs)

An investigational device is a medical device that is the subject of a clinical study

designed to evaluate the effectiveness and/or safety of the device. Clinical investigations undertaken to develop safety and effectiveness data for medical devices must be conducted according to the IDE regulations (21 CFR 812). Certain clinical investigations of devices (e.g., certain studies of lawfully marketed devices) may be exempt from the IDE regulations [21 CFR 812.2(c)].

Unless exempt from the IDE regulations, an investigational device must be categorized as either "significant risk" (SR) or "non-significant risk" (NSR). (Examples of each kind, published by FDA, are included in Appendix 8.) The determination that a device presents a non-significant risk or significant risk is initially made by the sponsor. The proposed study is then submitted either to FDA (for SR studies) or to an IRB (for NSR studies).The IRB's SR/NSR determination has significant consequences for the study sponsor, FDA, and prospective research subjects.

SR device studies must be conducted in accordance with the full IDE requirement (21 CFR part 812), and may not commence until 30 days following the sponsor's submission of an IDE application to FDA. Submission of the IDE application enables FDA to review information about the technical characteristics of the device, the results of any prior studies (laboratory, animal, and human) involving the device, and the proposed study protocol and consent documents. Based upon the review of this information, FDA may impose restrictions on the study to ensure that risks to subjects are minimized and do not outweigh the anticipated benefits to the subjects and the importance of the knowledge to be gained. The study may not commence until FDA has approved the IDE application and the IRB has approved the study.

In contrast, NSR device studies do not require submitting an IDE application to FDA. Instead, the sponsor is required to conduct the study in accordance with the "abbreviated requirement" of the IDE regulations [21 CFR812.2(b)]. Unless otherwise notified by FDA, an NSR study is considered to have an approved IDE if the sponsor fulfills the abbreviated requirements, which address, among other things, the requirements for IRB approval and informed consent, record-keeping, labeling, promotion, and study monitoring. NSR studies may commence immediately following IRB approval.

Once the final SR/NSR decision has been rendered by the IRB (or FDA), the IRB will determine whether or not the study should be approved, using the same criteria it would use in considering approval of any research involving an FDA regulated product (21 CFR 56.111). Some NSR studies may qualify as "minimal risk" studies, and thus may be reviewed through an expedited review procedure (21 CFR 56.110). However, FDA considers all SR studies to present more than minimal risk, and thus, full IRB review is necessary. In making its determination on approval, the IRB should consider the risks and benefits of the medical device compared to the risks and benefits of alternative devices or procedures.

Additional information about device studies can be found on the FDA web-site.

- Studies involving non-significant risk devices

  In the application to the HSB, the PI should (a) clearly explain why the sponsor believes the device presents no significant risk to study participants, (b) provide supporting information, such as reports of prior investigations, and (c) inform the HSB whether the FDA or any other IRB has made a risk assessment and what the

results of those assessments were. The HSB then will independently assess the risk of the investigational device to be used in the study. If the HSB agrees that the device poses no significant risk to subjects, the PI will not be required to obtain an IDE from the FDA to conduct the study. However, if the HSB believes that the device does pose significant risk to subjects, it will notify the PI, who then is required to notify the sponsor, within 5 business days, of the HSB's decision. The sponsor must then notify the FDA of the HSB determination. Investigations determined by the HSB to involve a significant risk device, will be reviewed according to the requirements described below. Following the HSB determination of the risk involved, the HSB will review the protocol to make a risk/benefit assessment and consider the acceptability of the consent form, as it does for non medical device studies.

- Studies involving significant risk devices

  Sponsors are responsible for making an initial risk assessment regarding an investigational device. By definition, a significant risk device is an investigational medical device that presents a serious risk to the health or safety of the research subjects. Such a device is:

  · intended for use as an implant; or

  · purported to be useful in supporting or sustaining human life; or

  · intended for a use that is of substantial importance in diagnosing, curing, mitigating or treating disease, or otherwise preventing impairment of human health; or

  · one that otherwise presents a serious risk to the health, safety, or welfare of subjects.

  PIs should clearly explain in their protocol whether the sponsor believes that a device poses a significant risk to subjects when used in the context of the research activity, and if so, why. In addition, the PI should inform the HSB of results of any FDA or other IRB risk assessment of the device and should provide any supporting information, such as reports of prior investigations or risk determinations. The HSB will then make its own assessment of the risk of the investigational device. If the board agrees that the device poses significant risk to research subjects, the investigator will be required to obtain an IDE from the FDA to conduct the study. Following the HSB determination of the risk presented, the IRB will make a risk/benefit assessment and determine the acceptability of the consent form in accordance with normal review procedures described in this manual. For additional information on how to obtain an IDE from the FDA, contact the HSB Administrator.

3. Investigational Drugs

Research involving experimental or licensed pharmaceuticals is regulated primarily by the FDA, whose guidelines for investigational use of a new drug can be found at this web site.

Investigational drugs include the following:

- Products that are not generally recognized as being safe and effective for any use under the conditions prescribed, recommended, or suggested by the FDA.

- Products that are already approved by the FDA as safe and effective for specific indications, but are being studied for new indications (or doses, strengths, or frequency) other than those that have been approved, e.g., off-label use.

4. Studies Involving Exposure to Ionizing Radiation

For research involving exposure to ionizing radiation from internal radionuclides or external radiation sources, the FDA regulations require that the research be reviewed and approved by a Radioactive Drug Research Committee (RDRC) as well as by the HSB. SNL does not have an RDRC; therefore, the actual dosing of radio-labeled compounds or otherwise exposing research subjects to ionizing radiation can not be allowed on-site at any SNL site. Exposing human research subjects to radio-labeled compounds or ionizing radiation must occur at a collaborating institution, and with the approval of that institution's IRB and their RDRC. The HSB will require copies of all documentation submitted to the collaborating institution's RDRC, as well as a copy of the RDRC approval letter. This documentation must be included in the submission packet to the HSB.

Any human research involving ionizing radiation requires that investigators use an IRB-reviewed and approved consent form. The consent form should clearly outline in lay language, the quantity, significance, and risk, if any, of the radiation absorbed dose. The dose is usually compared with background radiation, the occupational exposure limit of 5000 mrem per year, or radiation doses received from familiar medical procedures (e.g., a chest x-ray). The explanation should be written in terms that are understandable to a person with an eighth grade education.

5. Emergency Use of an FDA-Regulated Test Article

FDA regulations allow for the emergency use of an investigational drug, biologic, or device when an individual is in an immediately life-threatening situation for which no standard acceptable treatment is available, and there is not sufficient time to obtain HSB approval for use of the FDA-regulated test article [21 CFR 56.102(d)]. Medical personnel faced with the need for the emergency use of an investigational drug, biologic, or device will do so only under approved Health Services procedures. The FDA requires that emergency use of a test article be reported to the HSB within 5 working days [21 CFR 56.104].

6. Sponsor-Investigator-IRB Interrelationship

The interrelationship and interaction between the research sponsor (e.g., drug, biologic, and device manufacturers), the PI, and the HSB may be very complex. The regulations do not prohibit direct sponsor-HSB contacts, although that interaction customarily occurs through the PI, who generally provides the communication link between the HSB and the sponsor. Such linkage is agreed to by the sponsors and PIs when they sign forms FDA-1571 and FDA-1572, respectively, for drug and biologic studies or an investigator agreement for device studies.

There are occasions when direct communication between the HSB and the sponsor may facilitate resolution of concerns about study procedures or specific wording in an informed consent document. The PI should be kept apprised of the discussion.

FDA regulations require that a sponsor assure the FDA that a study will be conducted in compliance with the informed consent and HSB regulations (21 CFR 50 and 56). This requirement has been misinterpreted to mean that it is a sponsor's obligation to determine

HSB compliance with the regulations. This is not the case. Sponsors should rely on the PI, who assures the sponsor on form FDA-1572 for drugs and biologics or the investigator agreement for devices that the study will be reviewed by an IRB. Because PIs work directly with IRBs, it is appropriate that they assure the sponsor that the IRB is functioning in compliance with the regulations.

The HSB must notify an investigator in writing of its decision to approve, disapprove, or request modifications in a proposed research activity [21 CFR 56.109(e)]. This correspondence should be made available to the sponsor by the PI. This documentation provides the sponsor with reasonable assurance that the HSB complies with 21 CFR 56 and that it will be responsible for initial and continuing review of the study.

A sponsor may choose not to conduct, to terminate, or to discontinue studies that do not conform with the sponsor's wishes. For example, the sponsor, investigator, and HSB may reach an impasse about study procedures or specific wording in an informed consent document. The FDA will not mediate such disagreements. The FDA's policy of decentralized ethical review of clinical investigations allows such decisions to be made by local IRBs, and any disagreements between a sponsor, IRB, and PI should be resolved through appropriate communication among those parties.

7. Studies Involving Human Embryonic Stem Cells, Germ Cells, and Cell-Derived Test Articles

Note: SNL does not currently have a policy on when or whether to allow this type of research. Until such a policy is adopted, approval by Sandia's Executive Vice-President may be required in addition to HSB approval.

In vitro research using cell lines that are already derived and established, from which the identity of the donor cannot readily be ascertained by the investigator, may be eligible for expedited review.

Research using cell lines that are identifiable with a donor, including cells that retain links to coded information that would allow identification of donors, is generally considered human subject research and requires HSB review. If the investigator obtains a written agreement from the holder of the identifiable private information (e.g., the deriver of the cell line) such that information will not be released to the investigator under any circumstances, and that the research will be conducted within the terms of the applicable Assurance by all parties engaged in the research, the HSB may determine that an administrative review is sufficient. Investigators should contact the IRB Office for further information.

In addition to mandatory HSB review, all human subject research involving the use of cells derived from human embryos or fetal tissue is governed by 45 CFR 46 and may also be subject to FDA regulations.

All research involving human embryonic germ cells derived from human fetal tissue must be conducted in compliance with the NIH Guidelines for Research Using Human Pluripotent Stem Cells, section on fetal tissue (http://www.nih.gov/news/stemcell/).

All research and clinical trials involving human transplantation of cells or test articles, such as differentiated cells derived from human embryos or human fetal tissue, must be conducted in compliance with FDA regulations and Public Law 103-43, "Research on Transplantation of Fetal Tissue."

Clinical research involving the use of stem cells and stem cell derived test articles are subject to FDA's Investigational New Device (IND) regulations and all human studies conducted under INDs require HSB review. Researchers contemplating such trials should contact the Center for Biologics Evaluation and Review (CBER) at the FDA for specific advice regarding meeting these requirements. CBER can be reached at (301) 827-5102.

Appendix F

Additional Protection for Vulnerable Populations

Children (Minors)

Special ethical and regulatory considerations apply when reviewing research that involves children (anyone who has not yet reached the age of consent as defined by state law). The HSB may approve research involving children **only if** (a) the research falls into one of four categories based on degree of risk and benefit to individual subjects, **and** (b) special provisions (listed under each category below) are met (as determined by the HSB):

1. Research involving no more than minimal risk

   If the research presents no more than minimal risk, it may be approved **only if** adequate provisions are made for soliciting the assent of the children and the permission of their parents or guardians.

2. Research involving more than minimal risk, but presenting the prospect of direct benefit to the individual subjects

   If the research presents more than minimal risk, but the intervention or procedure holds the prospect of direct benefit for the individual subject, or by a monitoring procedure that is likely to contribute to the subject's well being, it may be approved **only if**:

   - the risk is justified by the anticipated benefit to the subjects, **and**
   - the relation of the anticipated benefit to the risk is at least as favorable to the subjects as that presented by available alternative approaches; **and**
   - adequate provisions are made for soliciting the assent of the children and permission of their parents or guardians.

3. Research involving more than minimal risk and no prospect of direct benefit to individual subjects, but likely to yield generalizable knowledge about the subject's disorder or condition.

   If the research presents more than minimal risk and does not hold the prospect of direct benefit for the individual subject, or by a monitoring procedure that is not likely to contribute to the well being of the subject, it may be approved **only if**:

   - the risk represents a minor increase over minimal risk, **and**
   - the intervention or procedure presents experiences to subjects that are reasonably commensurate with those inherent in their actual or expected medical, dental, psychological, social, or educational situations, **and**
   - the intervention or procedure is likely to yield generalizable knowledge about the subjects' disorder or condition that is of vital importance for the understanding or amelioration of the subjects' disorder or condition; **and**
   - adequate provisions are made for soliciting assent of the children and permission of their parents or guardians.

4. Research not otherwise approvable that presents an opportunity to understand, prevent, or alleviate a serious problem affecting the health or welfare of children

If the research does not meet any of the requirements set forth above, it may be approved **only if**: [45 CFR 46, Subpart D]

- the research presents a reasonable opportunity to further the understanding, prevention, or alleviation of a serious problem affecting the health or welfare of children; **and**
- the Secretary of the Department of Health and Human Services, after consultation with a panel of experts in pertinent disciplines (e.g., science, medicine, education, ethics, law) and following opportunity for public review and comment, has determined that the research satisfies either:
  - one of the conditions set forth above, or
  - all of the following conditions:
  - (a) the research presents a reasonable opportunity to further the understanding, prevention, or alleviation of a serious problem affecting the health or welfare of children
  - (b) the research will be conducted in accordance with sound ethical principles; and
  - (c) adequate provisions are made for soliciting the assent of children and the permission of their parents or guardians.

For more information regarding children as research subjects, see 45 CFR 46, Subpart D, "Additional DHHS Protections for Children Involved as Subjects in Research."

Pregnant Women and Fetuses

If pregnant women may be involved in a study, the protocol should include an assessment of the advantages and consequences of their inclusion in the study. Research involving the human fetus poses special concerns because the fetus is unique, yet has an inextricable relationship to the mother, and the fetus cannot consent to participate as a research subject.

In addition to the general review requirements, prior research with animal subjects and, if reasonable, research with non-pregnant persons should form the basis of the risk/benefit assessment for fetal research. PIs who propose research involving human fetuses are required to assure the HSB that they are seeking information not obtainable in any other fashion.

In Utero Research

Three circumstances may affect in utero research. In the first, the study is directed toward pregnant women, in which the fetus is indirectly involved in the research, while in the second, the study is directed toward the fetus. Finally, there are situations where both the pregnant woman and the fetus are the subjects of the research activity. The HSB may only approve in utero research when one of the following two criteria are met in addition to all other applicable institutional, federal, state, and local requirements.

- The purpose of the research is to meet the health needs of the fetus and is conducted in a way that will minimize risk (for example a new technique for fetal transfusions for Rh incompatibility); or
- The research poses no more than minimal risk to the fetus and the purpose of the activity is the development of important biomedical knowledge that is unobtainable by other means.

After lengthy review, the National Commission determined that there is no difference between the moral status of a fetus destined for abortion and that of a fetus that is expected

to be carried to term. Therefore, only those research procedures that are acceptable for fetus going to term may be performed in anticipation of abortion, to preserve the mother's right to change her mind about ending the pregnancy.

The consent of both parents generally is required for research involving the fetus. However, the father's consent is not required in the following circumstances:

- The research is designed to meet the health needs of the pregnant woman.
- The father is not competent.
- The father's identity or whereabouts cannot reasonably be ascertained.
- The father is not reasonably available.
- The pregnancy resulted from incest or rape.

Ex Utero (neonate) Research

Federal regulations indicate that a neonate (delivered fetus) is viable if, in the judgment of physicians, it is likely to survive to the point of sustaining life independently, given the benefit of available medical therapy. If the neonate is viable, the regulations for research involving children apply. [45 CFR 46, Subpart B]

A nonviable neonate is defined by the federal regulations as "an expelled or delivered neonate that, although it is living, cannot possibly survive to the point of sustaining life independently, even with the support of available medical therapy. Although it may be presumed that an expelled or delivered neonate is nonviable at a gestational age less than 20 weeks and weight less than 500 grams, a specific determination as to viability must be made by a physician in each instance." If a neonate is non-viable, 45 CFR 46, Subpart B applies to the research activity.

Research Involving Fetal Tissue

The use of dead fetuses, fetal material, and the placenta is gaining considerable attention due to the lifting of a moratorium on federally funded research involving the therapeutic transplantation into humans of fetal tissue obtained from induced abortions and from recent controversy over the use of fetal stem cells.

When the fetal tissue is derived from an abortion, the decision to terminate a pregnancy and the actual abortion procedures must be kept independent from the retrieval and use of fetal tissue. The timing and method of abortion should not be influenced by the potential uses of fetal tissue for transplantation or medical research.

Fetal tissue from induced abortions should not be used in medical research without the prior consent of the pregnant woman. However, the decision and consent to terminate pregnancy must precede discussion of the possible use of the fetal tissue in research and any request for such consent that might be required for that use. A woman's consent to donate fetal remains is sufficient for the use of fetal tissue. Consent should be obtained in compliance with state law and the Uniform Anatomical Gift Act.

Payments and other forms of remuneration associated with the procurement of fetal tissue are prohibited, except payment for reasonable expenses occasioned by the actual retrieval, storage, preparation, and transportation of the tissue.

Potential recipients of fetal tissues, as well as research and health care participants, should be informed about the tissues in question via the consent form.

The pregnant woman should be prohibited from designating the transplant recipient of the fetal tissue. Anonymity between donor and recipient should be maintained, so that the donor does not know who will receive the tissue, and the identity of the donor is concealed from the recipient and transplant team. Experimental transplants performed with fetal tissue from induced abortions provided by a family member, friend, or acquaintance should be prohibited.

See Appendix E, FDA Regulated Studies, for more information on research that involves fetal tissue, human embryonic stem cells, germ cells, and cell-derived test articles.

Prisoners

Prisoners are considered vulnerable because they are in a restrictive, institutional environment that affords little opportunity for making choices, earning money, communicating with outsiders, or obtaining medical care. The National Commission for the Protection of Human Subjects found that prisoners often volunteer for medical research as a means of access to a competent medical examination, because health care is woefully inadequate in most prisons. Because their autonomy is limited, prisoners may participate only in certain categories of research, and special precautions are needed to assure that their consent to participate is both informed and voluntary [45 CFR 46.302].

Prisoners may participate in the following kinds of research:

- Studies of the possible causes, effects, and process of incarceration and criminal behavior, if those studies present no more than minimal risk or inconvenience to the subjects;
- Studies of prisons as institutions, or of prisoners as incarcerated persons, if those studies present no more than minimal risk or inconvenience to the subjects;
- Research on conditions affecting prisoners as a class (e.g., research on hepatitis, drug addiction, sexual assaults, and other conditions more prevalent in a prison population than elsewhere), but only after the Secretary of Health and Human Services (DHHS), has consulted with experts in medicine, ethics, and penology and published a notice approving the proposed research in the Federal Register; and
- Research on practices that are intended, and reasonably likely, to enhance the well-being of the subjects; however, if some of the prisoners will be assigned to control groups that will not benefit from the research, then the study must first be approved by the Secretary of DHHS, after consultation with appropriate experts, as described above.

Appendix G

Procedure to Determine Review Frequency 🕮

If, during the initial review of a research protocol, the HSB determines that a study involves only minimal risk*, then annual review is sufficient. However, if the HSB determines that a study involves **more than minimal risk**, the following procedure is invoked.

Step	Action
1.	HSB determines aspects of potential risks: nature (physical, psychological, social, economic) severity (moderate, high, severe) probability (low, moderate, high) duration (temporary, permanent)
2.	HSB determines whether the following are factors in the study: • health and vulnerability of subjects involved • previously reported adverse events • investigator and research team experience with the proposed work • PI history (previous causes for concern)
3.	HSB assigns a review frequency that is appropriate to the risk.
4.	As an alternative (or in addition) to increased review frequency, the HSB may elect to implement the following measures: • Have an HSB member monitor the consent process. • Have an HSB member or third-party observe research activities. • Implement stronger controls to protect privacy and confidentiality • Interview subjects after participation

*The probability and magnitude of harm or discomfort anticipated in the research are not greater in and of themselves than that ordinarily encountered in daily life or during the performance of routine physical or psychological examinations or tests

Appendix H

Criteria for Determining Additional Monitoring

If a proposed study involves any of the following…:

A. unusual levels or types of risk to subjects or inclusion of subjects from a vulnerable population

B. a PI who previously failed to comply with the requirements of federal regulations or determinations of the HSB

C. a concern about possible material changes occurring without HSB approval based on information provided in continuing review or from other sources

…then the HSB must seek additional monitoring (beyond reports from the PI) to verify that the approved protocol is being followed and that no material changes have occurred since the previous HSB review.

The type and frequency of monitoring is determined by the following:

If research involves…	Then have an HSB member or third party monitor…
Criteria A	• PI research records quarterly or semiannually
Criteria B	• research activities quarterly • consent process quarterly • PI records monthly
Criteria C	• PI records immediately • research activities immediately
More than one criteria	• PI records immediately, then monthly • research activities immediately, then quarterly

Appendix I

Reporting Table

Research Involving Human Subjects

This table summarizes what must be reported during the course of any human subject research conducted by, for, or at Sandia National Laboratories. For details on reporting responsibilities and report content, contact the HSB Administrator at 845-9171 or treser@sandia.gov.

Note: Situations that indicate "immediate" or "prompt" reporting, must be done via phone or in person ASAP, and followed up with a written description via e-mail within 2 days. All other reporting must be done in writing within the timeframe allowed.

Who	Reports What	To Whom	When
PI	Any ***adverse event***[1]	HSB	within 1 week
	Any ***serious adverse event***[2]	HSB, sponsor	immediately
	Any ***unanticipated problem***[3]	HSB	within 2 weeks
	Deviation from approved protocol[4]	HSB	promptly
	Failure to comply with requirements[4]	HSB	
	Proposed change in approved protocol, including change of PI[5]	HSB	before change occurs – change must be approved by HSB
	Progress and status on active protocols[6]	HSB	annually, unless otherwise directed by the HSB
HSB	All serious adverse events[7]	DOE, sponsor	promptly
		OHRP	within 1 week
	All unanticipated problems[8]	SNL	promptly
		OHRP, sponsor	within 30 days of receiving PI report
	All ***serious*** or continuing ***non-compliances***[9]	SNL, DOE, OHRP, sponsor	promptly
	All suspensions or terminations of HSB approval of research[10]	PI, SNL, DOE, OHRP	promptly
	Any new proposal that includes: [11] • an institution without an established IRB • a foreign country • a potential for significant controversy • vulnerable populations *or* • classified or sensitive information	DOE	before HSB approval
	Changes in HSB membership[12]	DOE, OHRP	as they occur
	Complaints about research[13]	SNL, DOE	promptly
	Summary of approved research[14]	DOE	annually

DOE – Department of Energy Office of Science (SC-72) and local DOE Office as needed

HSB – Human Studies Board Administrator
OHRP –Office for Human Research Protections in the Department of Health and Human Services
PI – Principal Investigator
SNL – SNL Institutional Official

Definitions

Adverse event – Any undesirable incident, experience, or outcome associated with a subject's participation in the research, whether or not considered related to the research.

Serious adverse event – An adverse event that meets **any** of the following criteria

- results in death
- is life-threatening
- results in subject hospitalization
- results in persistent or significant disability/incapacity or other harm
- results in congenital anomaly/birth defect, or
- requires medical or surgical intervention to prevent one of the above outcomes

Noncompliance – Any failure to comply with applicable requirements (federal law, DOE directive, or HSB policy/procedure) to protect human subjects.

Serious noncompliance – A noncompliance is deemed serious if it affects the health, safety or well being of subjects, or if it constitutes a deviation from the HSB-approved protocol.

Continuing noncompliance – A noncompliance becomes continuing if it is repeated or additional noncompliances are associated with the same PI or organization.

Unanticipated problem -- Any incident, experience, or outcome associated with the subject's participation in the research that meets **all** of the following criteria:

(1) is unexpected given the research procedures and the subject population being studied

(2) is possibly related** to participation in the research

(3) suggests that the research places subjects or others at a greater risk of harm (including physical, psychological, economic, or social harm) than was previously known or recognized.

**there is a reasonable possibility this may have been caused by the research procedures

Examples

Unanticipated Problem

A PI conducting behavioral research collects individually identifiable sensitive information about illicit drug use and other illegal behaviors by surveying college students. The data are stored on a laptop computer without encryption, and the laptop computer is stolen from the PI's car on the way home from work. This constitutes an unanticipated problem and must be reported because the incident was (a) unexpected (the PI did not anticipate the theft); (b) related to participation in the research; and (c) placed the subjects at a greater risk of harm from the breach in confidentiality of the study data than was previously known or recognized.

Adverse Event that is Not Unanticipated

A PI is conducting a psychology study to evaluate the factors that affect reaction times in response to auditory stimuli. To perform the reaction time measurements, subjects are placed in a small, windowless, soundproof booth and asked to wear headphones. The HSB-approved protocol and informed consent document describe claustrophobic reactions as one of the risks of the research. The 20th subject enrolled experiences significant claustrophobia, resulting in the subject withdrawing from the research. This is not an unanticipated problem because the potential for claustrophobic reactions – in terms of nature, severity, and frequency – was expected and documented. This is reportable to the HSB, but not to DOE or OHRP.

Source of requirements identified in table

[1, 2, 3] 10 CFR 745.103(b)5, DOE 443.1A

[4] 10 CFR 745.103(b)5

[5] 10 CFR 745.103(b)4, DOE 443.1A

[6] DOE 443.1A

[7] 10 CFR 745.103(b)5, DOE 443.1A

[8] 10 CFR 745.103(b)4 and 5

[9] 10 CFR 745.103(b)5

[10] 10 CFR 745.103(b)4 and 5

[11] DOE 443.1A

[12] 10 CFR 745.103(b)3, DOE 443.1A

[13] DOE 443.1A

[14] DOE 443.1A

Notes

- This table does not include FDA requirements.
- Some reporting requirements vary with the funding source.
- These definitions and time frames are a compilation from several sources, including the OHRP Guidance issued 1/15/07.
- Terms like “promptly” and “immediately” are a little vague, but still connote a limited time span. The intent seems to be to allow a bit of wiggle room for both PIs and IRBs while still conveying a sense of urgency.

Appendix J

From OHRP draft guidance 10/24/06

Algorithm for Determining Whether an Adverse Event is an Unanticipated Problem